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Vol. 132, No. 4

ANNALS of SURGERY

A Monthly Review of Surgical Science and Practice

September and October Numbers
Contain Papers Delivered at
The Seventieth Annual Meeting
of the
AMERICAN SURGICAL ASSOCIATION
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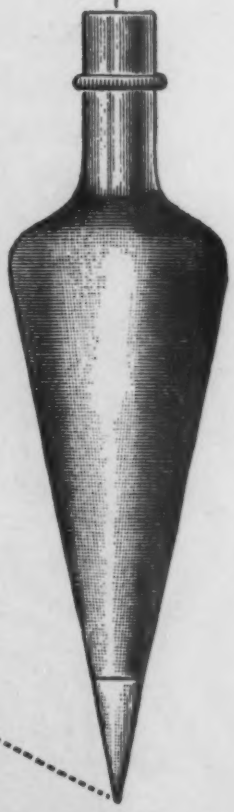

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ANNALS OF SURGERY

VOL. 132 OCTOBER, 1950 No. 4

THE OCCURRENCE OF ENDOCARDITIS WITH VALVULAR DEFORMITIES IN DOGS WITH ARTERIOVENOUS FISTULAS*

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In the course of some physiologic studies upon chronic cardiac failure in dogs we have used arteriovenous fistulas as an effective method for diminishing the cardiac reserve sufficiently. It was of interest to us to observe during these same studies that dogs with large arteriovenous fistula loads frequently died after some weeks of "spontaneous" endocarditis with severe valvular destruction, whereas in dogs with smaller arteriovenous fistula loads this complication was not observed. These observations invited our further investigation particularly because it has been found that endocarditis rarely occurs spontaneously in a variety of animals.[1] Likewise the finding of spontaneous endocarditis in the dog has been reported to be extremely rare.[2] It is because of this relative resistance to endocarditis among experimental animals that previously reported methods for the experimental production of endocarditis have usually involved one or, more frequently, both of the following factors:

1. The introduction of large numbers of bacteria, often supposedly type specific for endocarditis, into the animal by one or more of several possible routes.

2. Some form of direct injury to the heart valves.

Thus, Rosenbach[3, 4] was one of the first investigators to report the production of endocarditis experimentally. He utilized direct mechanical injury of the heart valves and injection of bacteria. Rosenow,[5] from his experimental and clinical studies, likewise suggested that endocarditis was usually an infection superimposed upon a previously injured heart valve. Welch[6] and his associates wounded the endocardium with a needle and resorted to accessory respiratory infection and dietary restriction, together with injection of massive doses of bacteria, in order to lower the resistance of their experimental animals

* This work was supported by a grant from the Life Insurance Medical Research Fund. Read before American Surgical Association at Colorado Springs, Colo., April 20, 1950.

and produce endocarditis. They were unable to produce endocarditis in their rabbits by bacterial injection alone. Also, in support of this contention, Kinsella and Muether[7] were unable to produce endocarditis in dogs by injecting stroptococci; however, after the heart valves were injured mechanically by a valvulotome passed down through the carotid artery, endocarditis could be produced by intravenous, and even oral administration of the organisms. Thus, Kinsella[8] has stated that two factors are necessary in every case of bacterial endocarditis, "a pre-existing injury of the valve, and a recent infection which may invade the blood stream." Willius[9] and Christian,[10] in recent reviews, appear to be in essential agreement with the above statement. The work of Nedzel[11] is of interest in this regard, for he showed that bacterial endocarditis may be produced experimentally by inducing pressor episodes in a dog by injections of Pitressin followed by injections of bacteria; and further that Pitressin pressor episodes in the absence of bacteria could produce lesions "characteristic of those found in the human heart in rheumatic endocarditis." Dreshfeld,[12] on the other hand, has reported the production (in rabbits) of endocarditis by bacterial injection alone without previous mechanical injury to the valves. Dick[13] also has been able to produce experimental endocarditis in 16 of 26 dogs by the use of repeated intravenous injections of large doses of *Streptococcus viridans* or beta hemolytic streptococcus. However, many of these dogs received continual injections of bacteria from one to six years. Blahd, Frank, and Saphir[14] observed bacterial endocarditis in 40 per cent of 25 dogs whose heart valves were not previously injured, following one or more injections of beta hemolytic streptococci isolated from the lung of a dog dying of pneumonia. Macneal and associates[15] have reported the successful transmission of bacterial endocarditis from man to rabbits by "repeated intravenous injection of large amounts of pure cultures in serum broth." They comment on the evident tendency for these lesions to heal. This observation has been noted by several authors,[5, 6, 16, 17] particularly those who have not utilized some form of direct injury to the heart valves together with their bacterial injections for endocarditis production.

It may be correctly surmised from this brief review of the literature on experimental endocarditis that injection of bacteria without or with some form of injury to the heart valves in order to increase incidence and severity of the infection, have constituted the most successful methods for production of experimental endocarditis. These studies have provided much valuable knowledge concerning the pathogenesis of endocarditis and have served to establish a definite link between bacterial infection and endocarditis. However, these same studies have left largely unanswered the fundamental question as to why, under certain conditions, bacterial infection appears to have such a predilection for endothelial surfaces, especially of the heart valves. It is concerning this latter question of the susceptibility of the heart valves to endocarditis that we believe the present studies, utilizing, as they do, a somewhat different approach

for the production of endocarditis, have served to emphasize several factors of importance in promoting this valvular susceptibility.

METHOD OF STUDY

Mongrel dogs, previously de-wormed and of either sex, were used in these studies. All animals were allowed a period of at least two months in the animal colony for purposes of acclimatization before they were utilized in these experiments. Animals not in good health for any reason at the end of this period of time were not operated upon. All of the dogs were fed a balanced diet of commercial dog biscuit supplemented daily with fresh horsemeat. Dogs of two estimated age groups were used. The criteria for estimating age have been described.[18] Group I consisted of young dogs—two to five years old; group 2, of old dogs—ten years or more of age.

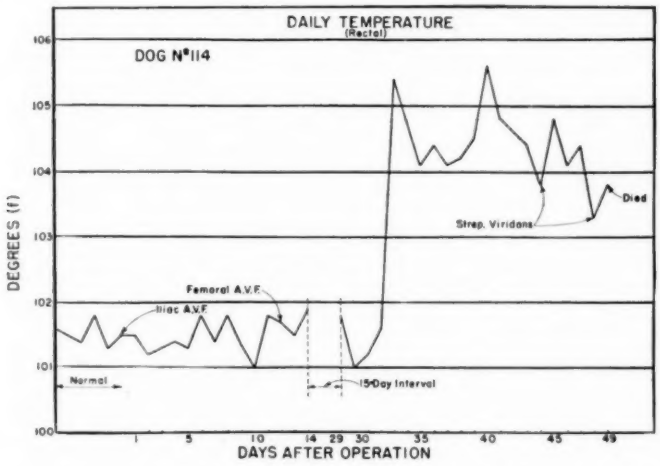


FIG. 1.—Temperature record of dog with large arteriovenous fistulas developing endocarditis. No bacteria were injected. Following construction of arteriovenous fistulas and prophylactic penicillin for one week, the only studies performed were daily temperature measurements and blood cultures as indicated. The clinical course of this animal is shorter than the average; otherwise typical.

All dogs not dying during the course of these experiments were sacrificed by intravenous pentobarbital. All animals used in these studies had an autopsy performed at the time of death.

OPERATIVE PROCEDURE

The arteriovenous fistulas were made surgically under aseptic conditions. Where more than one fistula was made in a particular dog, the operations were staged one to four weeks apart. The iliac fistulas were made immediately distal to the trifurcation of the abdominal aorta between the iliac artery and vein. The femoral fistulas were made 2 to 4 cm. below the inguinal ligament

between the femoral artery and vein. The aorta-vena cava anastomoses were made just proximal to the trifurcation of the abdominal aorta. In all cases the artery-vein anastomoses were made side-to-side, using a single running stitch of fine silk (6–0) on atraumatic needles. The lengths of all fistulas were measured at the conclusion of the anastomosis after release of the blood vessel clamps and again at autopsy. With only one exception (Dog 36)* all iliac and femoral fistulas were made 23 to 40 mm. in length. Since in all of these cases the diameter of the fistula substantially exceeds that of the parent artery, these minor differences in the length of the fistula can probably be disregarded in making comparisons. All animals were given prophylactic injections of penicillin in oil 150,000 units daily for one week following each operative procedure.

DIAGNOSIS OF ENDOCARDITIS

The term endocarditis is used in these studies to denote an inflammation of the lining of the heart, especially that overlying the valves. The diagnosis of endocarditis in these dogs has been based upon the observation of typical

TABLE I.—*Dogs With Large** Arteriovenous Fistula Loads and Endocarditis*

	Dog No.	Arteriovenous Fistula No.	Location	Days Survival After Fist. I	Fist. II	Cause of Death
A. Young age group (2 to 5 years)	114	2	Iliac-femoral	42	30	Endocarditis
	250	2	Iliac† Aorta-vena cava	98	60	Endocarditis
	124	2	Iliac-femoral	109	76	Heart failure (induced with NaCl)
	451	2	Iliac-iliac	112	27	Endocarditis
	26	2	Iliac-femoral	120	35	Endocarditis
	35	2	Iliac-femoral	121	63	Endocarditis
	24	2	Iliac-femoral	148	137	Endocarditis
B. Old age group (10 years or more)	6	1	Iliac	55	..	Endocarditis
	37	2	Femoral-femoral	81	69	Endocarditis
	36	2	Iliac-femoral	109	87	Sacrificed‡

** Fistula load *sufficient* for the development of endocarditis.
† Iliac fistula partially closed prior to making aorta-cava fistula.
‡ Endocarditis cured with aureomycin 2 months before sacrificed.

gross and microscopic findings within the heart at autopsy. However, it has been possible to make a diagnosis of endocarditis in almost all of these animals before death on the basis of the following criteria:

1. Development of fever.
2. Development of elevated blood sedimentation rate.
3. Development of heart murmurs, systolic and diastolic.
4. Observation of petechial phenomena (in eyes).
5. Recovery of organisms from the blood.

Figure 1 exhibits the febrile clinical course of one such animal with large arteriovenous fistulas developing endocarditis.

* Iliac fistula = 15 mm.

OBSERVATIONS ON THE PRODUCTION OF ENDOCARDITIS BY ARTERIOVENOUS FISTULAS

Following the construction of arteriovenous fistulas of sufficient size, it was necessary only to allow a minimum time of approximately four to six weeks to elapse for the development of endocarditis (See Fig. 1). During this period many but not all of these animals developing endocarditis had various physiologic studies, as outlined below, carried out. The incidence of endocarditis in the animals with arteriovenous fistulas is indicated in Tables I and II. Study of these tables indicates that there are several factors of importance in determining the development of endocarditis. These factors have been discussed in a previous publication,[19] but several of paramount importance are mentioned here:

TABLE II.—*Dogs with Small* Arteriovenous Fistula Load; Control Series (Young Age Group, Two to Five Years Old).*

Dog No.	Arteriovenous Fistula No.	Location	Days Survival After Fist. I	Fist. II	Results	Cause of Death
100	1	Iliac	1	...	No endocarditis	Died postop.
34	1	Femoral	30	...	No endocarditis	Sacrificed
70	1	Iliac	115	...	Living	No evidence of endocarditis
62	1	Iliac	124	...	Living	No evidence of endocarditis
101	1	Iliac	125	...	Living	No evidence of endocarditis
56	1	Iliac	126	...	Living	No evidence of endocarditis
59	1	Iliac	202	...	Living	No evidence of endocarditis
135	1	Iliac	237	...	No endocarditis	Sacrificed
79	1	Iliac	289	...	No endocarditis	Sacrificed
591	2	Femoral-femoral	355	350	No endocarditis	Sacrificed

* Dogs with arteriovenous fistula load *insufficient* for the occurrence of endocarditis.

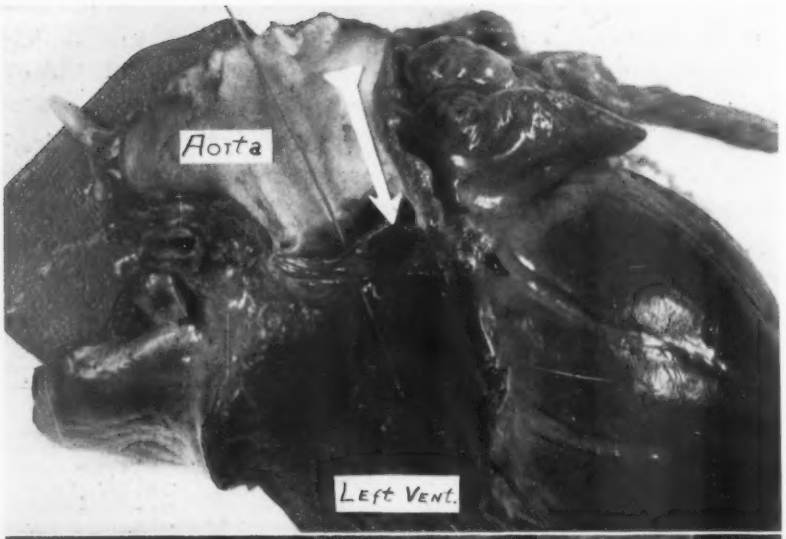
1. *The Relationship of the Arteriovenous Fistula Load to the Incidence of Endocarditis.* It has been our consistent observation in these studies that there is a very definite level to which one must increase the cardiovascular work load in order to be followed regularly by the development of endocarditis. With degrees of cardiovascular stress increase less than this level, the hearts remained immune to the development of "spontaneous" endocarditis. The relationships between degree of increased fistula load and the occurrence of endocarditis observed in these studies are indicated in Table III. The occurrence of heart failure has not been essential for the production of endocarditis.

TABLE III.—*Relationship of Arteriovenous Fistula Load and Endocarditis.*

Dog Age	Sufficient for Endocarditis	Not Sufficient for Endocarditis
Young (2–5 years)	One iliac plus One femoral, *or* Two iliac, *or* Aorta-cava. A.V.F.	One iliac *or* Two femoral A.V.F.
Old (10 years or more)	One iliac, *or* Two femoral A.V.F.	One femoral A.V.F.

2. *The Duration of the Fistula Load.* The duration of the arteriovenous fistula stress is of importance in the genesis of endocarditis. Following the

FIG. 2



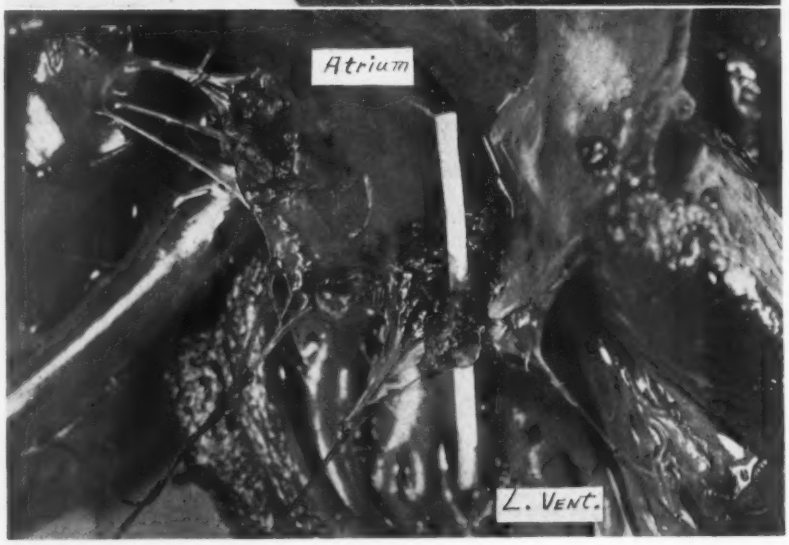


FIG. 3

FIG. 2.—Dog 114. Large vegetation on aortic valve resulting in perforation. The heart has been opened so as to leave the aortic tricuspid valve intact. The probe lies in the path of normal blood flow into aorta. The arrow points to the perforation. (Temperature record seen in Figure 1.)

FIG. 3.—Dog 24. Ulcerative bacterial endocarditis. Two large vegetations on the mitral valve leaflet, one of which has perforated.

introduction of an arteriovenous load sufficient* to be followed by endocarditis, the earliest that we have been able to diagnose the presence of endocarditis has been approximately one month. Moreover, in the group of ten dogs (Table I) with the larger arteriovenous fistula loads, which were sufficient in size to result in the spontaneous development of endocarditis, all have died within 148 days. In a group of ten other animals[19] with large fistula loads sufficient for endocarditis, but which did not develop endocarditis, the duration of life was significantly shorter. It is possible that they also would have developed endocarditis had they been allowed to survive longer. On the other hand in the ten dogs (Table II) with a small arteriovenous fistula load, none has developed endocarditis, although we have observed them as long as 355 days under

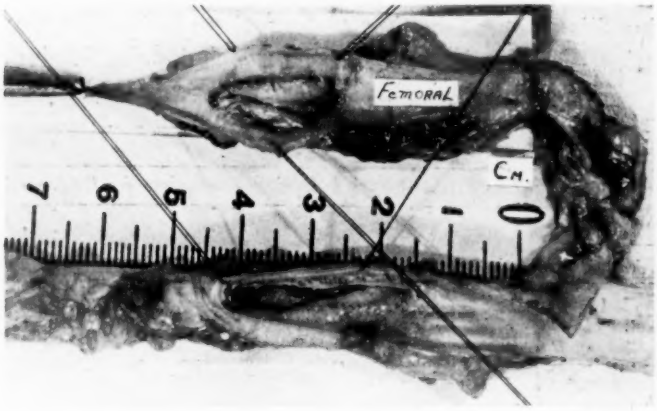


FIG. 4.—Dog 24. Iliac and femoral arteriovenous fistulas. (Valvular lesions seen in Figure 3.)

exactly similar conditions. Thus, it is apparent that the size and duration of the fistula stress are important conditioning factors for the occurrence of endocarditis. Approximately 75 per cent of the dogs with sufficiently large arteriovenous shunts existing for more than four weeks have developed a "spontaneous" endocarditis.

3. *The Age of the Animal.* In these experiments the age of the animal was important only in regard to the position of the fistulas. In old dogs bilateral femoral fistulas or a single iliac fistula resulted in endocarditis, whereas larger vessels needed to be involved in young dogs in order to be followed by endocarditis. However, by adjusting the size, position, and number of arteriovenous fistulas it has been possible to observe endocarditis in an equally high incidence in both age groups.

* Refer to Table III for definition of terms "sufficient" and "insufficient" as used in context in reference to arteriovenous fistula load.

PATHOLOGY*

Grossly, the valvular lesions varied in appearance from the soft friable vegetations morphologically similar to those seen in bacterial endocarditis in man to the firm smooth vegetations typical of rheumatic endocarditis. Damage to the point of actual rupture of the valve cusp has occurred frequently (See Figs. 2 and 3). Likewise, microscopically the pathologic changes in the heart valves show striking similarities to bacterial and to rheumatic endocarditis as seen in man. Often one leaflet may show only bacterial vegetations while another within the same heart shows only the rheumatic type. Occasionally these two different types of pathology were seen within different parts of the same leaflet. Vegetations were also found sometimes on the mural endocardium. All valves have been involved except the pulmonary, although not all valves were involved in every animal. Of the ten dogs which developed endocarditis during this study, at the time of death three had vegetations at the site of their arteriovenous fistulas while in the remainder the fistulas were clean (Fig. 4). The gross pathologic findings in the hearts of these dogs are summarized in Table IV.

TABLE IV.—*Valve Involvement and Infecting Organism in Endocarditis.***

Dog No.	Age	A. V. F. No.	A. V. F. Location	Aortic	Pathology	Mitral	Pathology	Tricusp.	Pathology	Organism
451	Yg.	2	I†, I	O	.....	+	Bacterial	O	.....	Not done
114	Yg.	2	I, F†	+	Bacterial	+	Rheumatic Bacterial	+	Rheumatic	*Strep. Viridans*
26	Yg.	2	I, F	+	Bacterial	O	.....	O	.....	*Aerob. Aerogenes*
250	Yg.	1	A-Vc.†	O	.....	+	Bacterial	O	.....	Not done
35	Yg.	2	I, F	+	Bacterial	+	Rheumatic Bacterial	O	.....	*Aerob. Aerogenes*
124	Yg.	2	I, F	O	.....	O	.....	+	Rheumatic	Not done
24	Yg.	2	I, F	O	.....	+	Rheumatic Bacterial	+	Rheumatic	Hemolytic Strep.
3 ‡	Old	2	I, F	O	.....	+	Scar Rheumatic	O	.....	*Aerob. Aerogenes*
6	Old	1	I	+	Bacterial	+	Rheumatic Bacterial	+	Hemorr. Bacterial‡	Not done
37	Old	2	F, F	O	.....	+	Rheumatic Bacterial	O	Hemorr. only	*Aerob. Aerogenes*
Total				4		8		4		

**Bacteriologic studies were made with the co-operation of Dr. W. W. Spink. "Bacterial" means "bacterial-like." "Rheumatic" means "rheumatic-like."

†I = Iliac A.V.F.

F = Femoral A.V.F.

A-Vc = Aorta-Vena Cava A.V.F.

‡ Blood cultures became negative and clinical condition indicated abatement of the active infection after aureomycin therapy.

One animal in this series with endocarditis (Dog 114) has been found to have a typical microscopic picture of acute proliferative glomerulonephritis†† in the kidneys.

* A morphologic study of these materials is nearly complete and will be published in co-operation with Professor B. J. Clawson, Dept. of Pathology, Univ. of Minnesota.

†† Verified by Professor E. T. Bell, Dept. of Pathology, University of Minnesota.

BACTERIOLOGY

In all but the earliest animals studied, repeated blood cultures have been made. These findings are summarized in Table V. In all dogs with endocarditis whose blood was cultured, organisms have been present in the blood. It has been of interest to us, however, that there appears to be nothing specific about the type of organism necessary to cause endocarditis, nor does there appear to be any relationship between the type of infecting organism and the type of pathology within the heart, *i.e.*, rheumatic-like or bacterial-like. The relatively high incidence of coliform bacteria suggests an endogenous source for the organisms in some instances.

It may be significant that the animal (Dog 114) mentioned above which developed glomerulonephritis was the only animal in the series with a *Streptococcus viridans* septicemia.

TABLE V.—*Relationship of Adrenal Gland Weight to Arteriovenous Fistula Size and the Occurrence of Endocarditis.*

	Dog No.	Sex	Weight of Adrenal Glands mg./Kg./Body Weight	
A. Normal Dogs	1	M	72.9	
	2	F	90.2	
	3	M	70.9	
	4	M	91.2	
	5	M	62.0	
	6	M	83.5	78.0 Mean
	7	M	77.7	
	8	M	87.5	
	9	F	76.2	
	10	F	68.5	
B. Large* A.V.F. with active endocarditis	114	M	104.5	
	24	M	92.8	
	35	M	141.5	
	37	M	100.0	
	451	M	166.6	**140.7 Mean**
	124	M	184.0	
	6	M	163.9	
	250	F	172.0	
C. Large A.V.F. with cured endocarditis	36	M	152.9	
D. Large* A.V.F. and no endocarditis	110	M	145.2	
	71	F	109.0	
	4	M	153.3	
	431	M	133.0	
	49	M	115.0	129.9 Mean
	17	M	163.5	
	69	M	147.0	
	130	F	98.4	
	47	M	105.0	
E. Small* A.V.F. with no endocarditis	591	M	84.7	
	135	M	64.9	77.0 Mean
	100	M	69.9	
	79	M	88.5	

* Definition of terms Large and Small A.V.F. contained in Tables I and II

ADRENAL WEIGHTS

It was noted early in the course of these studies that the animals which developed endocarditis had large adrenal glands. In all animals studied, the

adrenal glands have been weighed to the nearest milligram on an analytical balance soon after death. Results of these observations are denoted in Table V. From these data, it is apparent that endocarditis was associated with heavier than normal adrenal gland weights. Since the dogs with large arteriovenous fistulas which were sacrificed before they had developed endocarditis also had somewhat enlarged adrenal glands, it would appear that adrenal gland hypertrophy precedes the development of valvulitis. Further, those animals with small arteriovenous fistulas, which were insufficient to cause endocarditis, had adrenal glands of normal weight.

DISCUSSION

From the data presented, it is apparent that under the conditions of this experiment, dogs "spontaneously" developed a high incidence of severe endocarditis which progressed usually to death. This sequence of events differs materially from the type of experimental endocarditis which has been reported in the past.[5-7, 11, 15, 16] In the usual types of experimental endocarditis, as mentioned earlier, the infections have been produced by injection of large numbers of often supposedly specific organisms with or without some kind of mechanical damage to the heart valve. This type of endocarditis has usually been characterized by a lower incidence of animals infected, relatively less severe pathology within the heart, and a marked tendency for the endocarditis produced to heal. Since we have observed the fact that a relatively simple surgical procedure, viz.; arteriovenous fistulas between large vessels, leads to endocarditis in a high percentage of relatively resistant animals, the question immediately presents as to what conditioning factors associated with arteriovenous fistulas are acting to promote this increased susceptibility.

In addition to the stress of the arteriovenous fistulas, some of the animals were subjected to extra sodium chloride and/or work on the treadmill. However, not all of the endocarditis dogs were subjected to either of the above added stresses. Also some of the dogs in this study were subjected to various physiologic measurements. All but two of the dogs developing endocarditis had physiologic studies performed upon them involving vena puncture. Of the animals with smaller fistula loads showing no endocarditis, all but one had exactly comparable physiologic studies. While in all probability organisms were introduced adventitiously by these maneuvers, which were frequently performed with clean but not aseptic technic, the fact that the animals with the lesser cardiovascular stresses imposed showed no endocarditis seems to indicate that the primary factor in the susceptibility to endocardial infection is the cardiovascular stress. This contention is further supported by the fact that the two dogs (Nos. 114 and 250, Table I) with large arteriovenous fistulas which developed endocarditis even though no* vena punctures were performed, exhibited an endocarditis as severe as any of the other animals in the series.

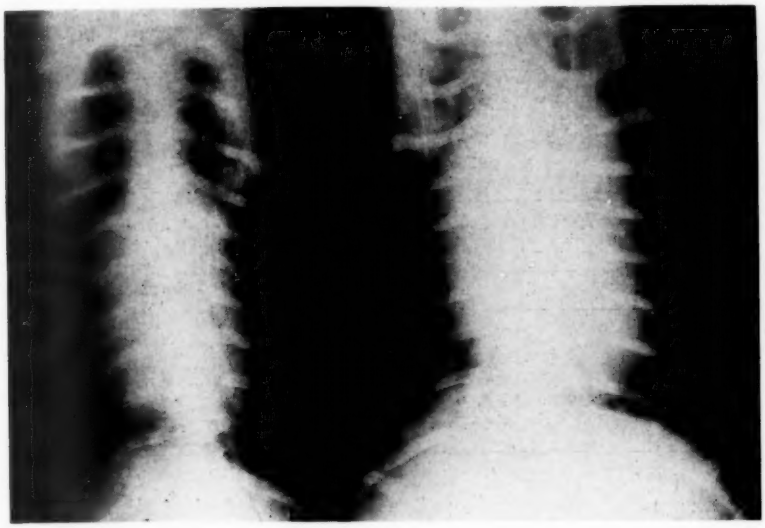
* Several blood cultures were drawn utilizing aseptic technic after the onset of fever.

The data derived from the physiologic studies mentioned above suggest that the susceptibility to endocarditis observed is related to two main factors:

1. A mechanical factor pertinent to the enormous increase in the work thrust upon these hearts by the large arteriovenous fistulas. Traumatic damage to the heart valves incident to increased output is included in this heading.

2. An endocrine factor due possibly to an imbalance or altered hormone secretion from the adrenal glands.

Obviously, the entrance of pathogenic organisms into the dog's body must occur. The route of entrance has not been determined.



A B

FIG. 5.—Dog 35. Six foot roentgenograms of heart. (A) As a normal. (Frontal area = 63 cm.^{2}) (B) Nine weeks after an iliac and femoral arteriovenous shunt. Endocarditis present at this time. Frontal area = 106 cm.^{2}

An arteriovenous fistula produces a lowering in the total peripheral resistance, the compensation for which is an increase in cardiac output. In our studies the cardiac outputs with the large fistula loads were elevated as much as six-fold (see example, dog 35, Table VI), as measured by the direct Fick procedure.* The cardiac silhouette as measured by planimetry from 6 ft. roentgen ray pictures was increased (Fig. 5). The plasma volume and total extracellular fluid space determinations also showed great elevations, the former up to 100 per cent and the latter by as much as 30 per cent (see example Dog 35, Table VII). A large fistula also produces a corresponding rise in pulmonary arterial pressure. Detailed reports on these observations will be made later, but it is obvious that each of these factors increases considerably

* Oxygen content of blood samples determined by the manometric Van Slyke method.

the mechanical work of the heart. It is perhaps of interest that the healthy human heart likewise is capable of similar augmentation in cardiac output, increases as much as nine times the basal rate having been recorded.[20] The present study does not indicate what changes as outlined above may be determining in the results observed. However, the increased mechanical work of the heart is obviously a central factor. The question is by what intimate mechanisms this change might influence the ultimate production of endocarditis. One observed fact, namely the increased adrenal weight at death in dogs developing endocarditis, is of interest in this regard. The dogs sacrificed early after bilateral fistula production and without endocarditis also showed large glands, indicating that the enlargement precedes the development of valvulitis. It is of interest that Selye[21] has postulated that rheumatic diseases represent an abnormal response of the endocrines to stress. It would not serve a useful purpose to speculate at this time about the mechanism by which the stress, the endocarditis, and the adrenal hypertrophy are interrelated, except to suggest

TABLE VI.—*Cardiac Output and Arteriovenous Fistulas; Dog 35, Young Age (Iliac + Fem. A.V.F. 5/3).*

Date	Condition	Cardiac Output CC./Min.
4/27	Normal	3,440
6/24	Iliac+fem. A.V.F.	17,800
7/6	Iliac+fem. A.V.F.+salt (failure)	7,630
7/21	Iliac+fem. A.V.F.+digitalis	24,420
7/29	Iliac+fem. A.V.F.+digitalis	18,720

that the inherent self-perpetuating characteristic of clinical endocarditis might be closely related to the adverse effects of cardiac stress upon the endocrine system and resistance to infection. Further studies of this relationship are in progress.

TABLE VII.—*Extracellular Fluid Changes With Arteriovenous Fistulas; Dog 35, Young Age (Iliac — Fem. A.V.F. 5/3).*

Date	Condition	Plasma Volume* (cc.)	Thiocyanate Space (Per cent of Body Wt.)
4/13	Normal	1095	39.2
4/21	Normal	1120	38
5/3	Operation	....	..
6/22	7 wks. postop.	2335	47
7/5	Failure	2265	52
7/11	Digitalis	2485	48
7/20	Digitalis	1975	41

* T-1824 method.

The occurrence, in one dog, of a typical glomerulonephritis associated with endocarditis appears to be of significance in the light of the frequent clinical association of these two entities.

SUMMARY

1. Observations have been reported in which, after the creation of large arteriovenous fistulas in dogs, endocarditis occurred without intentional introduction of bacteria.

2. Endocarditis occurred in about 75 per cent of dogs in which sufficiently large shunts existed for more than four weeks.

3. Adrenal gland enlargement followed creation of large arteriovenous shunts and preceded the development of the valvulitis.

4. Acute proliferative glomerulonephritis was observed in association with the endocarditis in one animal.

5. Other concomitant findings have been reported and discussed.

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PULMONARY ARTERIOVENOUS ANEURYSM*

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Although pulmonary atreriovenous aneurysm was recognized at autopsy by Churton[1] as early as 1897 and by Wilkens[2] in 1918, correlation of these lesions with a clinical syndrome leading to premortem diagnosis was apparently not made until 1939, by Smith and Horton.[3] The first reported surgical treatment, a successful total pneumonectomy, was carried out by Shenstone in 1942,[4] the patient having been previously studied and a diagnosis made by Hepburn and Dauphinee.[5] Since then over 50 cases have been recorded, many of them surgically treated, and it has become apparent that previous confusion of these lesions with congenital cyanotic heart disease, polycythemia vera and various benign lung tumors has delayed their recognition and appropriate surgical treatment.

An excellent and comprehensive survey of the literature, including some unreported case experiences, was published by Yater, Finnegan and Giffin in 1949.[6] It is the purpose of this paper to record our experience with an additional four patients, three of whom were treated surgically and each with a satisfactory outcome. The surgically excised lobes were prepared by vinylite-plastic bronchovascular casting technic,[7] and the results illustrated and summarized (Figs. 2, 4 and 6).

CLINICAL CONSIDERATIONS

The clinical syndrome in the fully developed case of pulmonary arteriovenous aneurysm is quite readily recognized. The essential points are cyanosis and clubbing in the presence of a normal heart, together with roentgenographic findings of a vascular tumefaction in the lung fields.

Cyanosis may however be entirely absent (*e.g.*, Cases 1 and 4). It usually appears in childhood, but sometimes rather abruptly in adult life. Dyspnea is slight at first but may be progressive. The "squatting" tendency observed in congenital cyanotic cardiacs has been described in one reported case.[45] Clubbing of the fingers and toes is nearly constant, if cyanosis is present, and usually noted to have about the same time of onset. It may be associated with arthralgic pains[8] and with a radiologic demonstration of pulmonary osteo-arthropathy. Bleeding from the nose is a common complaint (Cases 1 and 4), less commonly oozing from superficial cutaneous or visceral hemangiomas.[9] Hemoptysis may occur to a severe degree and may be lethal.[10]

* Aided by a Grant from the Office of Naval Research, Project N6ori Task Order XI. Read before the American Surgical Association, Colorado Springs, Colo., April 20, 1950.

Symptoms of central nervous origin may be experienced, especially when the polycythemia is well developed. These include headache, vertigo, weakness, syncope, convulsions, paresis or paresthesia of the extremities, dysphagia and thickness of the speech.

A few patients have been aware of some discomfort in the chest, and an abnormal fremitus. Actual chest pain is not common unless a complicating adhesive pleurisy exists,[8] a not uncommon operative finding. General weakness, lassitude, and loss of weight have all been described; the latter has been quite marked in some cases (cf. Case 3).

The *physical findings* are principally those of cyanosis in variable degree and clubbing of the digits, but one or both of these may be absent (Case 1). In about half of the reported cases multiple "spidery" telangiectasia and discrete nodular hemangiomas of the face, neck, lips, mucous membranes or trunk are encountered, emphasizing the relationship to hereditary telangiectasia of the Rendu-Osler-Weber type (*e.g.*, Cases 2 and 4). Despite cyanosis and dyspnea, the heart is usually found to be normal in size, shape, and free of organic murmurs, except in cases with terminal decompensation or unrelated cardio-vascular disease (Cases 2 and 3). Blood pressure recordings are usually normal, as is the venous pressure by direct measurement, although veins of the retina, head, and neck may appear prominent. On auscultation over the site of the aneurysm there may sometimes be heard a continuous rough humming murmur accentuated in systole and in deep inspiration (Cases 3 and 4). In rare instances the murmur may be exaggerated by forced expiration.

In contradistinction to polycythemia vera, the spleen is normal in size or only suggestively enlarged.

LABORATORY FINDINGS

Typically there is an increase in erythrocyte count and hemoglobin content of the blood. In some cases these have been observed to increase over a period of observation. Values as high as 11.45 million red cells,[11] and 24.9 Gm. hemoglobin[12] have been recorded. In a small minority the red cell count and hemoglobin are normal or low; in the latter situation there will usually be a history of repeated epistaxis, hemoptysis, or unrelated causes of anemia. The hematocrit level tends to follow the polycythemia.

The total blood volume in the polycythemic cases is of course elevated, but the plasma volume shows little or no increase, in contradistinction to the findings with peripheral arteriovenous fistula.[3] Cardiac output is not usually increased.[13, 45]

The peripheral arterial oxygen saturation is usually decreased, even as low as 63 per cent,[13, 45] and decreasing further with exercise. The actual blood oxygen content may be relatively high due to the polycythemia.

The venous circulation time is normal, and biochemical studies of the blood plasma show no significant deviations from normal, unless a decrease in carbon-dioxide.

DIFFERENTIAL DIAGNOSIS

1. *Polycythemia rubra vera.* In this disease the age group is generally older; there is splenomegaly, with abnormalities of blood and bone-marrow morphology, with immature white cells and basophilic stippling of red cells. It is noteworthy that spherical homogeneous densities may appear in the lung fields during the course of this disease, as first demonstrated by Hirsch.[15] Such pulmonary lesions tend to be multiple, evanescent, and do not demonstrate vascular continuity on the hilar side.

2. *Congenital heart disease* is a possible mis-diagnosis. In pulmonary arteriovenous aneurysm the cyanosis is frequently of later development; the heart size and contours are normal, and murmurs are usually absent except for a bruit over the lesions themselves. The roentgen evidences of vascular tumors are absent in the congenital cardiac, unless proximal aneurysm or diffuse dilatation of the pulmonary arteries exists. These shadows are then hilar in type.

3. *Tuberculosis.* Pulmonary arterial aneurysms of a local type occur in tuberculous cavities, the so-called Rasmussen aneurysms[16] and very rarely dissecting aneurysms of the parenchyma.[17] These are hardly to be confused in the presence of active tuberculous symptoms and positive sputum.

4. *Benign Pulmonary Tumors.* These are not commonly associated with cyanosis and polycythemic changes, although clubbing may be marked. In this connection Arel and Saka[18] reported multiple mycotic tuberculous thrombosing aneurysms in a case with negative sputum, strongly simulating tumors of a discrete, and benign type.

ROENTGEN AIDS TO DIAGNOSIS

The roentgenographic features essential for the diagnosis of arteriovenous aneurysm are (1) a saccular, cirsoid or racemose cluster of sharply defined structures with homogenous density and (2) demonstration of enlarged tributary vascular channels. These features may be shown in standard radiographs, but usually are better demonstrated by laminagraphy, which also permits differentiation of the arterial and venous trunks, particularly when the lesion is situated in a lower lobe.

Changes in intrathoracic pressure as produced by the Valsalva and Müller tests are helpful in demonstrating the vascular nature of the lesion. More than half of the published articles describing the use of these tests report a positive response; that is, a reduction in size during the Valsalva maneuver. Two of the present series showed this (Figures 1B, 1C), the other two being inconclusive, since the appropriate radiographs were not made. The measured changes, when present, were more pronounced in the tributary channels than in the aneurysm proper. Pulsation during radioscopy is said to be an uncommon finding. No significant pulsations were noted in the present series.

Angiocardiography showed rapid filling of the malformation, usually one or two seconds after Diodrast reaches the right atrium. Prompt clearing of

the opaque medium from the lesion would be expected, but usually the aneurysm remained opacified after the pulmonary arteries had cleared.

Actual demonstration of successive filling of arteries and veins may be of value, and identification of anomalous origin of the tributary artery or insertion of the tributary vein is likely to be of practical interest to the surgeon. Small arteriovenous aneurysms, overlooked in the preliminary roentgenograms, may be intensified by Diodrast and thereby recognized. Since multiple pulmonary aneurysms occur in many cases, it is the radiologist's duty to recognize them, because the presence of more than one lesion may influence the surgeon's decisions on operability and on conservation of lung tissue. These considerations suggest a limited angiocardiographic technic, using large films and a standard stereo chest cassette changer, the two exposures being made at two and four seconds respectively. This would permit a more complete search of the lung fields than is possible with the newly developed rapid film advancer.

TREATMENT

The existence of an arteriovenous pulmonary aneurysm, even in the absence of symptoms, cyanosis or polycythemic changes, is sufficient indication for recommending surgical treatment, unless the patient has some forbidding unrelated pathology. This decision is based on the significant danger of serious or lethal hemoptysis[10] and fatal hemothorax.[2, 19] In the presence of marked cyanosis and polycythemia there are additional hazards of cardiac and cerebral anoxia, and thrombotic complications. One case of subacute bacterial endarteritis has been reported[13] and two cases of complicating brain abscess.[20, 21]

A therapeutic problem is posed by the tendency toward multiplicity in these lesions (*e.g.*, Case 4). In 27 of Yater's collected cases more than one aneurysm was recognized; others may possibly have escaped detection radiologically. If the lesions are multiple in a single lobe (Case 2) or contiguous lobes, the surgical problem is simpler. Bilateral multilobar lesions demand conservative local surgery, such as first practised by Janes.[22]

The surgical method of attack in the recorded cases has varied from simple ligature of the supplying artery or arteries, local dissection, and lobectomy to the extreme of total pneumonectomy. The enormous size of the lesions *"in vivo,"* and the remarkable dilatation of both afferent arteries and efferent veins may lead to a decision for radical surgery where lobectomy might suffice on more prolonged study and dissection.

Conservative or medical management has included repeated venesections, drugs such as phenylhydrazine, and artificial pneumothorax.[23] The latter has been proved to be of no therapeutic value, either in reducing size of the lesion or in ameliorating the polycythemia. It has inherent danger, as the lesions are superficially placed, thin-walled and adherent, because of the possibility of tearing and bleeding.

During operation upon the severely polycythemic cases, transfusion usually is undesirable, and supportive therapy consists of glucose solutions, saline, or plasma. In preparation for operation, as in congenital cyanotic cardiacs, it may be wise to practise phlebotomy, reserving the blood for possible postoperative transfusion. This procedure was used in our second case. Frequent postoperative checks on the erythrocyte count and hematocrit are desirable to control the therapy.

In the dissection of the involved lobe or lobes, caution must be observed to detect anomalous vascular patterns. In our second case, although the aneurysm lay in the lower lobe, an artery to the lateral segment of the middle lobe arose from the lower lobe vascular trunk and traversed the oblique fissure, leading to a decision for bilobectomy. In one reported case[23] there was an absence of the upper lobe vein, all venous return passing through a single posterior inferior vein.

Ligation or transection of the supplying artery without dissection of the aneurysm has been practised, but with doubtful results. On theoretic grounds this is an objectionable procedure, since it should be a stimulus for the development of bronchial collateral circulation, which might prevent the anticipated local thrombosis, producing a bronchial-pulmonary arterial shunt of some magnitude. Where this type of simple ligation has been practised, the lesion persisted by roentgen-ray.[24]

PATHOLOGIC CONSIDERATIONS

Our three lobectomy specimens were prepared by bronchovascular injections of colored vinylite plastic.[7] The three specimens and resultant casts had certain features in common and some minor differences. In all instances the aneurysmal sac approached the visceral pleura closely, and in Case 1 actually elevated this membrane in the fashion of a vesicle. Cases 1 and 3 showed single sacs; in Case 2 two separate aneurysmal loops were present in close relation to one another. In the immediate vicinity of the aneurysms the supplying vessels were larger than at a more proximal level, but even at their proximal origins they were of greater caliber and thinner-walled than normal.

Vessels of more than one bronchopulmonary segment were sometimes involved, and there was no regularity whatever in the number and arrangement of the constituent arteries and veins. In none of the specimens were communications observed proximal to the aneurysmal sac, as reported by Goldman.[25] Communications existed only in the sacs which showed multiple openings. The diameters of supplying arteries at point of entrance into the sacs varied from two to eight millimeters. The draining veins in each case were larger than the corresponding arteries. There was no evidence in the casts of a significant contribution from the bronchial arteries. In Case 3 where these vessels seemed slightly enlarged, they apparently functioned merely as vasa vasorum.

In Case 2 sizable peripheral venous branches draining presumably normal pulmonary parenchyma emptied directly into the aneurysmal sac (Fig. 4A).

During systole, at least, the pressure may have been higher in the proximal (sac) ends of these veins than in the pulmonary capillaries which they drained, thus producing a momentary stoppage or even a reversal of flow.

Evidence supporting the congenital origin of these lesions, or an extremely slow developmental rate, is gained from the observation that the contiguous bronchi and parenchyma were but little disturbed, being intimately interlaced between the vessels and about the aneurysmal sac. The sacs were analogous in their position to capillaries, as Hayward and Reid[26] pointed out. Yet they must be considered as more than dilated capillaries, since each aneurysmal sac was supplied and drained by more than a single artery and vein. Indeed some of the larger sacs were found to be entered directly by sizable peripheral venous branches, draining areas of capillaries which were in turn supplied by arterial branches not involved directly in the aneurysmal lesion.

DISCUSSION

These arteriovenous communications of the lung appear homologous with certain cavernous hemangiomas seen elsewhere in the body. As Reid[27] and Virchow[28] before him pointed out, they represent large channels joining arteries and vein. Albrecht[29] has referred to such cavernous hemangiomas as hamartomas, implying thereby that they represent more an error in development than a neoplasm.

The strikingly high incidence of cutaneous, mucosal and visceral angiomas in the reported cases, the frequent occurrence of telangiectasia or recurrent epistaxis in parents or siblings, the report by two authors of pulmonary arteriovenous aneurysm in brothers,[14, 25] all point toward the hereditary nature of these pulmonary lesions and their identification as a variant of Rendu-Osler-Weber disease (hereditary hemorrhagic telangiectasia).

Requiring explanation is the observation that a well-developed arteriovenous aneurysm may exist in the absence of cyanosis, clubbing, polycythemia, or other signs and symptoms (cf. Case 1). Likewise to be explained are the occasional case records in which cyanosis, clubbing, and polycythemia first appeared late in adolescence or in adult life. Sweet's case[12] of middle lobe arteriovenous neurysm was known to have had a normal hemogram two years before a surgical procedure. At the time of surgery, however, the red cell count had risen to over seven million, and the hemoglobin to 21.5 Gm. These observations pre-suppose either a hemodynamic block in a pre-existing arteriovenous communication or, what is more likely, a progressive increase in the size of the communications and in the degree of right-left shunt of venous blood with the passage of time.

SUMMARY

The clinical and diagnostic features of pulmonary arteriovenous aneurysm have been reviewed from the standpoint of the recorded cases, and from a

personal experience with four additional cases, three of which were treated by lobectomy. The pathologic anatomy of the lesions has been studied and illustrated by using the vinylite-plastic injection technic.

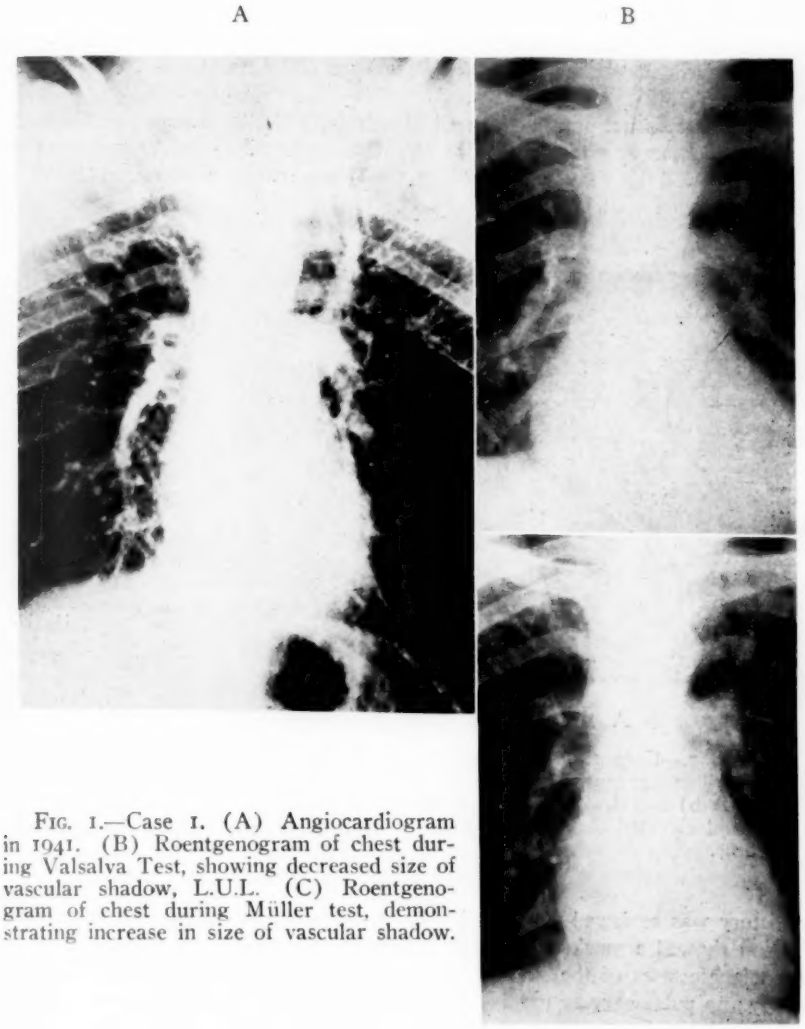


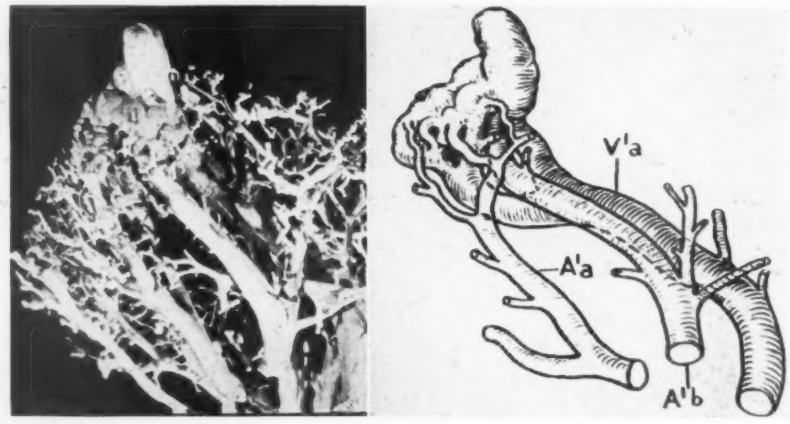
FIG. 1.—Case 1. (A) Angiocardiogram in 1941. (B) Roentgenogram of chest during Valsalva Test, showing decreased size of vascular shadow, L.U.L. (C) Roentgenogram of chest during Müller test, demonstrating increase in size of vascular shadow.

CASE REPORTS

Case 1.—(N. H. H., B20727) A. B., a 24-year-old white machinist was referred to the out-patient service on October 4, 1941, with a presumptive diagnosis of minimal pulmonary tuberculosis involving the left upper lobe. The lesion had been uncovered 3 weeks previously during routine roentgen ray examination for Army service. The patient was asymptomatic. He denied any pulmonary disease or tuberculosis contact. System review revealed frequent bouts of epistaxis as a child, occurring with lessened frequency as he grew older. Family history was not remarkable.

Upon physical examination his temperature was 99, pulse 64, respiratory rate 24, blood pressure 118/70, and weight 140 lbs. No positive findings were noted in the chest; there was an incidental finding of hypospadias. A tuberculin test was negative at 1.0 mg. O.T. Chest films indicated enlargement of the pulmonary vascular shadow in the left hilum extending as a tapering shadow into the apex. Laminagraphic studies confirmed this impression, demonstrating a division of the abnormal vessel into two large branches. Angiocardiograms were obtained, the first ever performed at the New Haven Hospital. They demonstrated conclusively the vascular character of the left upper lobe lesion (Fig. 1A).

The patient was not seen again until March 14, 1949, he having been inducted into the armed forces, serving for four years of active combat duty in the European theater. During this period he remained well. At this examination, an arterial blood sample revealed an oxygen content of 18.8 vols. per 100 cc., or 95 per cent saturation. The



A B

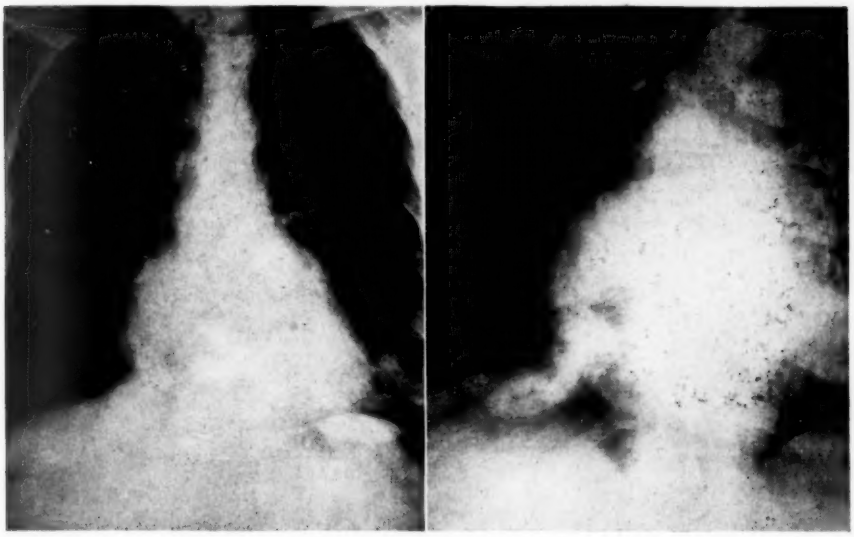
FIG. 2.—Case 1. (A) Bronchovascular vinylite cast (trimmed) photograph. The aneurysmal sac, supplied by the two apical segmental arteries (A_1a, A_1b) and drained by a single vein (V_1a), possessed an extremely thin wall and elevated the visceral pleura as a bleb. (B) Diagrammatic sketch of same.

family history was reviewed again, and did not reveal any bleeding tendencies. Physical examination showed a marked deviation of the nasal septum with a large spur. There were no telangiectases of the skin or visible mucosal surfaces. There was no cyanosis or clubbing; no pulmonary or cardiac murmurs. The erythrocyte count was 4.36 million, with a hemoglobin of 15.0 Gm. An electrocardiogram was normal. Chest roentgenograms were unchanged as compared with 8 years previously. The Valsalva and Müller signs were both positive (Figs. 1B and 1C). A diagnostic pneumothorax was performed, showing a separation of the upper lobe and its contained lesion from the parietal pleura.

On May 17, 1949, the patient was explored through the fifth intercostal space. A large pulsatile vascular tumefaction of the upper lobe was discovered, and a lobectomy carried out without drainage. Postoperatively the patient had a slight elevation of temperature for 3 days, and required 2 thoracenteses. On the fourth day after operation, nose blowing brought on a moderate epistaxis, which was controlled by packing. The patient was discharged from the hospital on the tenth day. When last seen 4 months after operation he was well and had gained 9 lbs. in weight.

Surgical Pathology No. 47360 (Figs. 2A, 2B). Beneath the pleura at the very apex of the lung was a thin-walled vesicle resembling an emphysematous bleb, but filled with blood. Examination of the lobar hilum showed both apical* arteries and vein to be greatly enlarged and thin-walled. In the cast made with vinylite plastic, the overall dimensions of the aneurysmal sac were 3 by 2½ by 2 cm. It received at least 3 small arterial branches from A_1a, a larger branch from A_1b, this having a diameter of 2 mm. at its point of entrance. Venous drainage was entirely into V1 by one large and several small channels. Delicate bronchial branches passed through the meshes of the interlacing arteries and veins, producing depressions on the surface of the aneurysmal sac, but the bronchi were themselves only slightly distorted.

Case 2.—(N. H. H. C35665) S. E. K., a 56-year-old housewife, was first admitted on December 20, 1949, with a life-long history of cyanosis and dyspnea. Three years previously she had a single episode of moderately severe hemoptysis. Chronic cough,



A B

FIG. 3.—Case 2. (A) P. A. Roentgenogram. (B) Angiocardiogram.

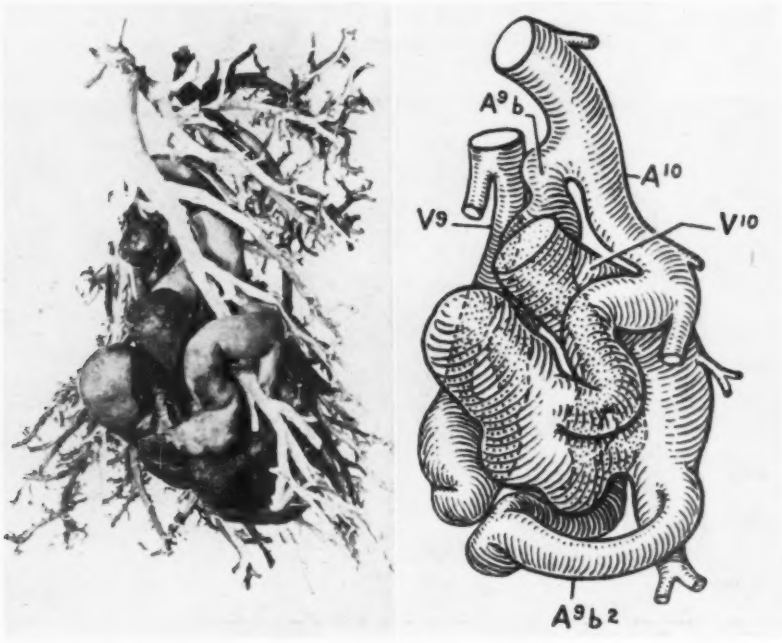
sputum, and chest pain were denied. After contracting rheumatic fever at age 18, the patient had valvular disease and was known to have fibrillated for many years. Two and one-half years before this admission, the patient was treated conservatively at another hospital because of a saddle embolus. This left the patient with persistent severe pain and burning sensations in the right foot, with claudication of the right leg. The family history was not available in detail.

On physical examination the patient appeared somewhat obese, with obvious cyanosis of the lips, tongue, buccal mucosa, and nailbeds. Moderate clubbing of the fingers and toes was present. Her temperature was 98.6, pulse (apical) 80, respiratory rate 24, and blood pressure 130/80. The chest revealed no abnormal breath sounds or bruit. The heart was enlarged to the right with an apical systolic and diastolic murmur. The cardiac rhythm was irregular. The liver was palpable two finger-breadths below the costal

* For this and the following descriptions both the Jackson-Huber nomenclature and the Boyden numerical designations will be used.

margin. No femoral pulses were detectable bilaterally although there was a faint dorsal pedis pulsation in the left foot. The right leg and foot were cool, slightly edematous, and there was a rapid onset of pallor with elevation. Neurologic examination was negative. Roentgenograms of the chest (Fig. 3A) revealed left auricular and ventricular enlargement and several large lobulated densities in the posterior basilar portion of the right lower lobe with a bandlike density extending to the hilum. An angiocardiogram verified the vascular nature of the lesion (Fig. 3B).

The erythrocyte count was 6.29 million, the hemoglobin 18.8 Gm., the white count 6,750 with a normal smear and differential. The hematocrit was 53 mm. An arterial blood specimen contained 17.87 vols. per 100 of oxygen, or 78 per cent saturation.



A B

FIG. 4.—Case 2. (A) Postero-medial aspect of trimmed right lower lobe cast. Two separate vascular loops are shown. Situated beneath artery (A_9b_2) is a peripheral venous tributary, draining into the aneurysmal sac from capillaries of a parenchymal area which has a normal pulmonary arterial supply. (B) Diagrammatic sketch of same.

After breathing 100 per cent oxygen the content was 19.29 vols. per 100. On the night before operation, 250 cc. blood was removed by venipuncture, citrated, and administered during operation. On January 3, 1950, after resection of the right seventh rib, a large tense aneurysmal sac was found in the lower lobe. There was a distinct systolic thrill to palpation of the lesion. Because of an anomalous arterial branch passing from the lower lobe transfissurally to the middle lobe, a bilobectomy was performed. The main lower lobe vein measured about 3.5 cm. in diameter. Since ligation of this large vessel did not appear quite safe, it was followed distally, and two smaller but still very large branches ligated and transfixed. The pleural cavity was drained with a catheter, which was removed on the fourth postoperative day. The postoperative course was smooth and almost afebrile. The patient left the hospital on the fifteenth day after operation.

When seen on February 10, 1950, the patient had no cyanosis, and there was improvement in her exercise tolerance. The erythrocyte count was 3.54 million, and the hemoglobin 10.5 Gm. There was little if any subjective improvement in the claudication and foot pain.

Surgical Pathology. No. 49264 (Figs. 4A, 4B). The lesion involved the vessels of the lateral (B9) and posterior basal (B10) segments. The dimensions of the lesion were 9½ by 4½ by 3½ cm. Two major arteriovenous loops existed. The smaller aneurysmal sac occurred between a branch of A_9b and V_9. The larger sac was more complex and received 3 large arterial channels. Two of these were branches of A_9b. The third and largest, a branch of $A_{10}b$ measured 8 mm. in diameter at its entrance into the sac. Venous drainage was entirely into V_{10}, which measured 15 mm. at the point where it left the aneurysmal sac. A larger sac on the postero-medial aspect of the lobe had a diameter approximately one and a half times greater. Small peripheral branches, venous in type, entered the major sac in its most prominent aspect. These venous branches drained capillaries of the parenchyma supplied by arterial branches not otherwise involved in the lesion. The segmental bronchi ramified through the meshes of the vascular plexus and showed no ectasia or other significant change, although they curved somewhat around the vascular dilatations.

Case 3.—(N. H. H. C32336) H. N. C., a 54-year-old white housewife was first seen in the out-patient clinic on October 13, 1949, because of dizziness, flushing, sweating, and nervousness. These symptoms had been present for about 6 years, of increasing frequency and severity for 2 years. There had been no episodes of fainting, or convulsions, but occasional throbbing headaches were noted,and recent exertional dyspnea. There had been a steady weight loss of 20 lbs. in 2 years. The menopause occurred 6 years previously. For 15 years the patient was known to be hypertensive. Details of the family history were only vaguely remembered, and not considered reliable. The patient had had a radical mastectomy in a private clinic 15 months previously with a diagnosis of carcinoma, and no mention had been made of pathology in the chest at that time.

The physical examination revealed a small but well-developed and nourished female who did not appear ill, except for mild cyanosis of the lips and nailbeds. The pulse was 72, the temperature 99, respiratory rate 18, and blood pressure 250/130, after rest in bed 180/110. The retinal vessels were tortuous with no scarring or hemorrhages of the fundi. A left mastectomy scar was well healed with no evidence of local recurrence. There was slight dullness and diminished breath sounds over the right lower lobe posteriorly. A harsh bruit was heard in the auscultatory triangle synchronous with the peripheral pulse. The heart was enlarged to the left but without murmurs. There was minimal clubbing of the fingers. Neurologic examination was negative.

Roentgenograms of the chest (Fig. 5) revealed transverse enlargement of the cardiac shadow, moderate pulmonary emphysema, and a long lobulated density in the basilar portion of the right lower lobe, thought to represent an arteriovenous aneurysm. Angiograms were technically unsuccessful. Laboratory data were as follows: R.B.C. 6.55 million, Hgb. 15.9 Gm., Hematocrit 45, W.B.C. 5500. Urine was negative for albumin and sugar; the sediment showed occasional red and white cells but no casts. The N.P.N. was 30, total serum protein 6.6 Gm., chlorides 96.9 mEq. and CO_2 26.8. The arterial oxygen saturation at rest was 73.2 per cent and after breathing pure oxygen 94 per cent.

An electrocardiogram revealed slight left axis shift with abnormally slurred limb leads and an abnormally depressed RS-T segment in lead V-4. The T-waves were inverted in lead V-4 and diphasic in leads I and V-6. The venous circulation time (arm to tongue) was 22 seconds. The blood serology was negative.

On January 12, 1950, the patient was explored after resection of the right seventh rib. A tense pulsating tumor of the right lower lobe was readily palpated but not easily seen. A resection of the right lower lobe and a very small middle lobe was performed,

the latter necessitated by an air leak in its proximal bronchus. The pleural cavity was drained; the postoperative temperature ranged between 100 and 101 F. for 3 days, and there was left-sided chest pain for a similar period. The patient was discharged on the thirteenth day. On this date the arterial oxygen saturation was 96.8 per cent at rest, and 100 per cent after re-breathing oxygen. A postoperative red cell count was 4.4 million with a hemoglobin of 12 Gm., and a white count of 7300. The bruit previously heard on the posterior chest wall was no longer present.

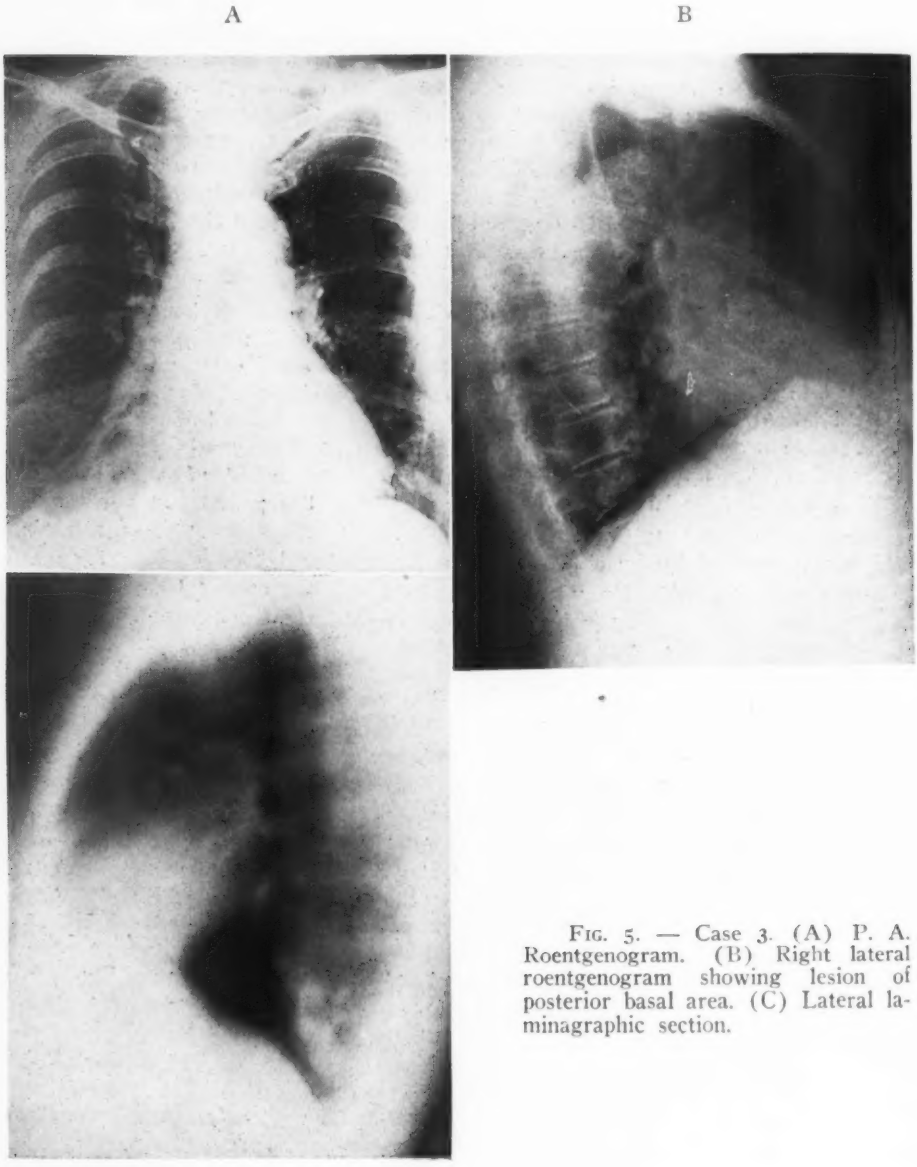


FIG. 5. — Case 3. (A) P. A. Roentgenogram. (B) Right lateral roentgenogram showing lesion of posterior basal area. (C) Lateral laminagraphic section.

Surgical Pathology No. 49333 (Fig. 6). A single aneurysmal sac measuring 3.5 by 2.5 by 2.5 cm. occupied the lateral basal segment. It was supplied by one large and several minute branches of A_9b, and was drained by two large and several small tributaries of V_9 and a small branch from V_{10}. Both A_9 and V_9 were greatly enlarged, the former measuring 8 mm. at the point of entrance into the aneurysmal sac, which was close to the diaphragmatic pleura. The associated vessels had a plexiform angiomatous arrange-

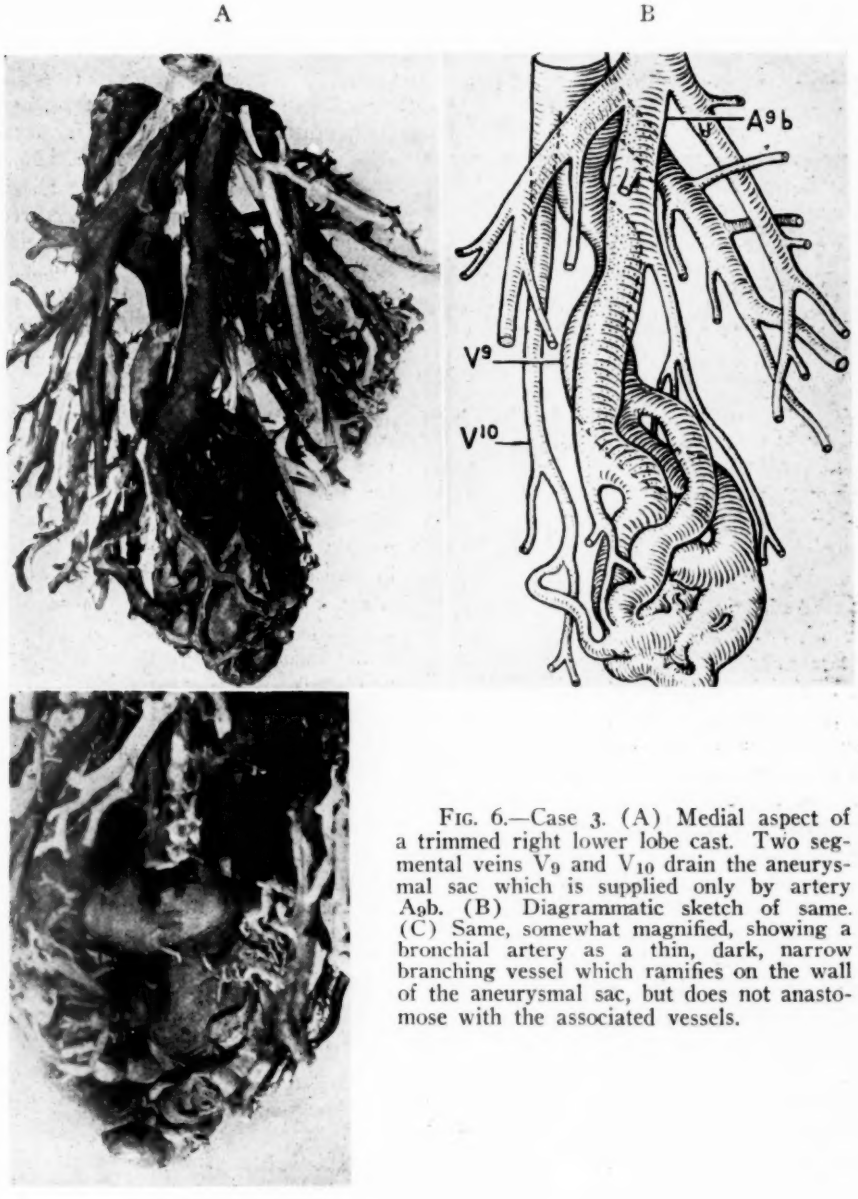


FIG. 6.—Case 3. (A) Medial aspect of a trimmed right lower lobe cast. Two segmental veins V_9 and V_{10} drain the aneurysmal sac which is supplied only by artery A_9b. (B) Diagrammatic sketch of same. (C) Same, somewhat magnified, showing a bronchial artery as a thin, dark, narrow branching vessel which ramifies on the wall of the aneurysmal sac, but does not anastomose with the associated vessels.

ment between the interstices of which the segmental bronchial branches penetrated. The bronchi were not abnormal in any way. A moderately enlarged bronchial artery followed the course of B_9 and was distributed upon the walls of the dilated vascular channels in the manner of a vas vasis, but without macroscopic communication with the arteriovenous complex (Fig. 6C).

Case 4.—(N. H. H. No. 48908) D. K., a 55-year-old white housewife was admitted to the hospital for the fourth time on February 5, 1949, because of chronic osteomyelitis of the right leg. For two days she had noted malaise, chills, fever, and headache. The osteomyelitis began in 1926. During 3 subsequent admissions to the hospital she was submitted to multiple drainages and sequestrectomies. There was a history of tonsillectomy at age 6, appendectomy at 15, right salpingo-oophorectomy for cyst at 24, and a similar procedure on the left for hemorrhagic cyst at 29. Dating from childhood the patient had frequent profuse epistaxes which seemed to be more severe after the artificial menopause. The epistaxes necessitated transfusions in 1924 and 1944. The family history revealed that two daughters had episodes of epistaxis from childhood and showed telangiectases of the conjunctivae, lips, and hands.

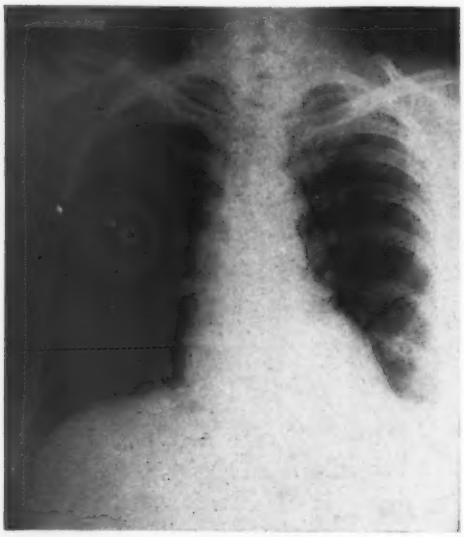


FIG. 7.—Case 4. P. A. Roentgenogram showing lesions at both lung bases.

Physical examination revealed a temperature of 99.2, pulse of 96, respiratory rate of 24, and blood pressure of 110/70. Cyanosis was not observed. Numerous spiderlike petechial areas were noted beneath the fingernails, in the conjunctivae, in the skin of the wrists, ankles, and trunk, together with small telangiectases of the lips, tongue and buccal mucosa. The ocular fundi showed scattered white punctate scars. There was a harsh systolic bruit at the left scapular angle. The heart rhythm was regular and no murmurs were heard. The fingers and toes were clubbed. The right leg was shortened with numerous scars, and ankylosis of the knee and ankle joints. Neurologic examination was normal.

The admission complaints disappeared in a few days and the skin petechiae faded, but there was no change in the telangiectatic lesions. Five blood cultures showed no growth, and lumbar puncture gave normal results. Chest roentgenograms (Fig. 7) revealed a cluster of fairly discrete, rounded densities noted particularly in the left lateral projection lying posteriorly in relation to the enlarged vascular markings. Similar small densities were found in the right cardiohepatic angle. On fluoroscopy the left-sided lesions gave positive Valsalva and Müller signs. Angiocardiography was not done. The erythrocyte count was 4.05 million with a hemoglobin value of 10.0 Gm. The hematocrit was 40. Stool examination revealed a positive guaiac test on two separate specimens. The Rumpel-Leede and Göthlin tests were negative. Red cell fragility was normal, as were the bleeding and clotting times. Arterial oxygen was 11.9 vols. per 100, representing 87 per cent saturation. An electrocardiogram was interpreted as normal.

The patient returned to her home in the West after the ninth hospital day without surgical treatment.

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DISCUSSION.—DR. WILLIAM E. ADAMS: My remarks will be confined chiefly to the presentation by Dr. Lindskog, who I think gave us an excellent report on this problem which we are seeing more frequently in recent years.

Although we have had experience with three of these patients, only one of the three had a large enough shunt to give rise to the characteristic blood picture changes and other physiologic findings. The one case was operated on first in 1943, at which

time a left pneumonectomy was done for a multiple A-V shunt. Outside of developing an empyema of the remaining pleural space two and one-half years later, for which a thoracoplasty was done, he remained quite well until 1948.

At that time, on a routine fluoroscopic examination, it was observed that he had a shadow appearing in the lower part of the right lung field [Slide]. A study of his blood picture showed an increase of his red cell mass, with increased hematocrit and hemoglobin. During the subsequent year, several studies were made, and these changes became increasingly greater.

As you see in the lower left-hand picture, the shadow in the right lung field remained somewhat the same although probably a little decreased in size.

Shortly before his second operation an angiocardiogram was made which showed not one but three separate A-V fistulas of the saccular type.

The upper one—in the far upper right corner of the lower right-hand film—was seen at the time of his first operation, but it was very small. It has increased very considerably in size.

After a considerable amount of study by our physiologist, Dr. John Perkins, and Dr. Carlson and Dr. Charbonne, working with me, we decided to explore his remaining lung, which was done with an oximeter in place, and recorded the degree of blood oxygen saturation.

[Slide] During the operation it was shown that the degree of saturation raised quite abruptly when the lower two shunts were obstructed, and again when the upper shunt was obstructed, thus elevating his saturation from approximately 73 to approximately 94 per cent.

[Slide] This table shows the blood picture before and after the two operations. As you see, the red cell mass was considerable before each one.

The red cell count was 7.2 million and the hematocrit 82 before the first operation. These figures were 7.19 and 75 before the second operation. In each case, however, the blood picture reverted toward the normal after each operation.

I agree with Dr. Lindskog that these cases do not always produce the characteristic —or what was thought to be the characteristic—picture of a large shunt of blood, with the resultant massive changes within the blood and other physiologic changes. I have the feeling that most of these fistulas developed from previously existing vascular anomalies of the lung which have caused no trouble until the shunt becomes considerable.

In view of the fact that they are likely to be bilateral—in which case a large amount of the lung may need to be sacrificed—one must keep in mind that conservation of lung function is very important in their management.

Dr. Brian B. Blades: During the past six years, I have operated upon three cases of arteriovenous fistula of the lung. There was a total of seven fistulas in the three cases.

[Motion picture] This motion picture will demonstrate the gross appearance of an arteriovenous fistula of the lung. These lesions have the appearance of a blood blister, are usually visible on the surface of the lung, and the pulsation in the lesion is evident.

In one of our cases, the clinical manifestations of arteriovenous fistula of the lung which have been described were present in the advanced stages. In the second case with bilateral fistulas, there were no changes in the laboratory findings, but a machine-like murmur could be heard over the lesion on one side. In the third case, in which there was a single fistula, there were no clinical manifestations of the disease.

I should like to agree with Dr. Lindskog and Dr. Adams that conservation of lung tissue is extremely important in the management of these cases.

Dr. Emile Holman: These very instructive and provocative studies of Dr. Lillehei come to me with considerable surprise, and I am wondering if there are not some local

factors peculiar to Minneapolis responsible for them. I am reminded of Elias Cooper, who in 1858 ligated the external iliac artery successfully, and who transferred his surgical activities in the midst of a very active practice from Illinois to California in 1853, where he founded the first medical college on the Pacific Coast. Very soon he wrote home that he was opening knee joints, wiring the olecranon and performing many operations without the development of laudable pus, and he suggested that it was the salubrious climate.

We have been making observations on arteriovenous fistulas for well-nigh 25 years. We have had specimens of hearts and fistulas of five and seven years' duration to examine, and we have never met this type of infection in the hearts. It is true that we have been greatly bothered with infection in the early postoperative course, and have seen infection at the site of the fistula followed by pulmonary infarcts and death from infection. We noted, however, that in every instance this infection was associated either with an infection in the operative wound or with an infection elsewhere in the animal incurred in fights and coincidental injuries.

Likewise, we have been frustrated in experiments on the lung for many years by infection from any wound of the animal incurred in the course of the experiment, so that we lay great stress on very careful closure of the operative wound, so that no suture presents on the surface, providing an opportunity for infection. No suture may be put through the skin in closing it without incurring the possibility of local infection, a small stitch abscess or even an infection that is not noted as an infection, but only as delayed healing.

I would suggest that these studies be correlated with evidence of infection in the animal, either of the operative wound or such as may occur following a fight with another dog, or following any surface wound.

DR. HERBERT C. MAIER: I should like to make a few comments on Dr. Lindskog's excellent presentation.

I would like to point out that occasionally there may be involvement of the chest wall in patients with the pulmonary arteriovenous fistula. As has been mentioned, multiple hemangiomata may be present in various portions of the body as well as in the lung. Moreover, occasionally large blood channels from the chest wall or diaphragm may enter into the pulmonary arteriovenous fistula. If this chest wall inflow is not controlled before the pulmonary veins are ligated, large amounts of blood may accumulate in the segment of lung being resected, and also serious hemorrhage from the chest wall may occur.

In one case we had a lesion in the chest wall on one side and a pulmonary arteriovenous fistula in the lung on the opposite side. Interestingly, in that case, there was notching of the ribs from the chest wall arteriovenous fistula, such as we usually associate with coarctation of the aorta.

In another of our cases, which has been reported in the literature, the patient presented herself with a positive blood culture, and we assumed that she had a bacterial endarteritis superimposed on her pulmonary arteriovenous fistula. She was treated by chemotherapy and the resection of the lobe containing the arteriovenous fistula was not performed until some months later, when the bacterial infection of the blood-stream had been quiescent for several months. That patient is well, some three years after the lobectomy. Cardiac catheterization was done prior to operation, and in that particular instance, the patient having marked cyanosis, the blood flow through the fistula was approximately 58 per cent of the total pulmonary blood flow; yet she had no increase in the pulmonary artery pressure, due to the low resistance in these pulmonary arteriovenous fistulas.

Another patient with pulmonary arteriovenous fistula but without any cyanosis or polycythemia, who has been followed for three years without operation—and in whom we are quite certain of the diagnosis on the basis of the X-ray findings and a ma-

chinery murmur—has had no symptoms or change in the blood count in that period of time.

DR. CLARENCE CRAFOORD: There is one point which has not been touched upon by the previous speakers, about which I would like to say a few words. We have encountered nerve symptoms in one of our cases, and it has also been mentioned in some of the cases published in the literature. I am speaking of attacks with sudden loss of consciousness, epileptic fits and transitory paralysis of certain groups of muscles. In our case these symptoms appeared repeatedly in connection with hemoptosis.

The origin of these symptoms has been discussed. We think that they are due to air embolism at the same time as the hemoptosis occurs. In connection with one attack in the case we had, we could observe small air bubbles in the retinal vessels.

I would also like to stress the importance of conservative treatment of the lesion with only local excision if possible. It is infinitely better to have a bloodless field when this excision is made. We have described this operation in connection with excision of other benign lesions of the lungs, and it is made after dissection and temporary clamping of the main vessel, the pulmonary artery and the veins, and also the bronchus with the bronchial arteries.

DR. C. W. LILLEHEI (in closing): I would like to thank Dr. Holman for his interesting discussion. I should also like to add the fact that it has been a source of speculation to us also, that in the light of the large amount of work that has been done with arteriovenous fistulas, that this unusual increased susceptibility to infection with a predilection for the heart valves has apparently not been previously noted. However, I should like to mention in this regard the fact that many of these previous studies with arteriovenous fistulas have concerned themselves with shunts either too small or of too short a duration in our experience to result in endocarditis. It is of interest perhaps that there are scattered case reports in the clinical literature in connection with arteriovenous fistulas (Surgery, **26:** 928, 1949; J. A. M. A., **141:** 130, 1949; Ann. Surg., **124:** 123, 1946; J. A. M. A., **126:** 766, 1944; Tr. A. Am. Physicians, **50:** 228, 1935) and also with shunts due to congenital heart lesions (H. B. Taussig, Congenital Malformations of the Heart, The Commonwealth Fund, 1947, New York.) that indicate a definite increased susceptibility in these conditions to endarteritis and/or endocarditis.

Moreover, experiments now in progress indicate that these animals with large arteriovenous fistulas are extremely susceptible to the intravenous introduction of small numbers of bacteria. Uniformly, they have developed a fatal endocarditis of the types described today with doses of bacteria that are completely innocuous to dogs without shunts.

Dr. Holman mentioned the problem of wound infection in these animals which, of course, is always a problem in the experimental laboratory. There was not time to mention in the formal presentation today, but in the text it will be noted that all animals were treated for one week with penicillin in oil (150,000 units/day) after each operative procedure, with no apparent effect upon the incidence of endocarditis. Likewise, most all of these wounds healed per primum. However, the important point, I believe, and the one I tried to emphasize today, is not so much where the bacteria are coming from, but rather their predilection only for dogs with large shunts and only for the heart valves. Whatever conditions might exist in the laboratory, it is obvious that the dogs with small arteriovenous fistulas, and who did not acquire endocarditis, had the same opportunity to acquire organisms as did the dogs with large shunts, and who subsequently did develop endocarditis.

Studies also in progress at the present time indicate that there is a difference in eosinophil responses to epinephrine, adrenocorticotrophic hormone, and cortisone between dogs with large and small ateriovenous shunts. It is of interest in this regard that Selye as long ago as 1944 suggested the possibility that rheumatic endocarditis

might be a response to stress. (J. A. M. A., **124**: 201, 1944.) It has occurred to us in some of our recent studies that perhaps the bacteria, themselves, are just another form of stress and that maybe foreign protein would be just as effective in causing the changes seen in these animals.

In conclusion, these studies have raised a number of interesting problems, the further investigation of which, we hope, may elucidate some of the clinical problems at present associated with these diseases.

DR. GUSTAV E. LINDSKOG (in closing): Without prolonging the discussion, I want to thank the individual speakers—Dr. Adams, Dr. Blades, Dr. Maier and Dr. Crafoord. Dr. Adams has emphasized again the tendency to multiplicity of these lesions. In more than 50 per cent of the reported cases they have been two or more in number, and that dictates the necessity for conservation in resection.

One point that has not been brought out is the extreme frequency of middle lobe involvement in these lesions. It doesn't appear in our own case material, but as one goes over the literature, one finds a disproportionately large number of middle lobe cases. Dr. Blades' graphic demonstration by moving picture film is certainly a contribution, and emphasizes the technical problem that can exist in these cases. Chest wall involvement, of course, is a part of the picture of disseminated telangiectasia and hemangioma.

As for Dr. Crafoord's comment, we have in our final paper, for publication, included the problem of the central nervous system symptoms and lesions, but did not have time to present them this morning.

A CLINICAL STUDY OF RESPIRATORY EXCHANGE DURING PROLONGED OPERATIONS WITH AN OPEN THORAX*

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THE ENDEAVOR OF EVERY SURGEON should be to carry his patient through an operation with the least possible disturbance of normal physiologic processes. Opening the thorax to obtain adequate exposure for upper abdominal operations has become commonplace. The physiologic disturbances produced by opening the thoracic cavity thus become of immediate concern to every surgeon utilizing a thoracic, or a thoraco-abdominal, incision. Beecher[1] has recently reported that severe respiratory acidosis may occur during the course of an operation with an open thorax. In an endeavor to obtain additional information concerning the altered conditions produced by opening the thorax, the following clinical study of respiratory gas exchange has been made.

METHOD

The present study is based on a series of 53 patients undergoing prolonged operations with an open thorax. The operations may be classified into three main groups: 13 pneumonectomies, nine lobectomies, and 31 miscellaneous operations. The 31 miscellaneous operations all involved an open thorax through a thoracic or a thoraco-abdominal incision, but in none of these patients was pulmonary tissue resected. A majority of these operations were esophagectomies, esophago-gastrectomies, or exploratory thoracotomies. Arterial blood samples were analyzed for oxygen content and capacity, carbon dioxide content, and pH. Arterial blood samples were drawn at the following times: (1) before the administration of the anesthetic; (2) after the patient was anesthetized and just before the pleura was opened while the respirations were still spontaneous and unassisted; (3) toward the end of the operation after several hours of controlled mechanical respiration with the pleural cavity open; and (4) one or two hours after operation with the patient in bed in an oxygen tent. Not all samples were obtained in every patient.

Anesthesia. The usual premedication was Sodium Pentobarbital, 0.1 Gm. the night preceding operation and an equal amount two hours before operation. Ten milligrams of morphine and 0.6 mg. atropine sulfate were given one hour preceding operation. A 7 or 9 mm. intratracheal tube with an inflatable cuff was introduced under topical Pontocaine anesthesia, or, in a few instances,

* Read before the American Surgical Association, Colorado Springs, Colo., April 19, 1950.

under intravenous Sodium Pentothal anesthesia. If the tracheal tube was introduced under local anesthesia, general anesthesia was then induced with intravenous Sodium Pentothal. Anesthesia was continued with ether and oxygen in a closed rebreathing circuit. In the first few patients in the series, Sodium Pentothal was the sole anesthetic agent used. Ether was not used in these patients in order to avoid the technical difficulties of blood gas analysis when small amounts of ether were present in the blood sample. Later these difficulties were overcome.[5] The patient was then placed in a lateral position. The diseased lung was uppermost for the lobectomies and pneumonectomies. The esophagectomies and esophagogastrectomies were performed through a left thoracic or a left thoraco-abdominal incision. Nothing was placed beneath the thorax and the operating table was not broken, as is sometimes done in order to facilitate exposure by arching the upper hemithorax.

Respiration was unassisted until the parietal pleura was exposed. When the pleura was opened, the patient was given 3 to 6 mg. of d-Tubocurarine.[8] At this time, mechanical insufflation of the lungs was started by use of either the Mautz[6, 7] attachment to the standard Heidbrink machine, or the Crafoord[4] apparatus. The principle of these machines is the same. In each, the rebreathing bag is encased in an airtight container slightly larger than the fully inflated rebreathing bag. At the end of the inspiratory phase, a large outlet valve immediately releases the pressure upon the rebreathing bag, and the expiratory phase occurs into the flaccid rebreathing bag without resistance. The pressure used to compress the rebreathing bag can be read on a water manometer and is easily controlled by a valve. The pressure used was generally 10 cm. of water. This intermittent insufflation of the lungs was continued throughout the operation until the pleural cavity was closed. Additional d-Tubocurarine was given during the course of the operation in amounts sufficient to prevent the respiratory muscles from opposing the mechanical insufflation of the lungs. No curare was administered toward the end of the operation, and the patients immediately resumed spontaneous respiration when the pleural cavity was closed, at which time mechanical respiration was discontinued. Secretions were aspirated from the trachea when indicated during the course of the operation and in the postoperative period.

Blood Samples and Chemical Methods. A Cournand arterial needle was inserted into the brachial artery under local anesthesia before inducing general anesthesia. The arm was bandaged on a splint, and the needle was left in place until the postoperative blood sample had been drawn. If the needle became dislodged before the last blood sample was obtained, the remaining samples were drawn from the femoral artery. The blood was collected under oil in a syringe containing a small quantity of heparin to prevent coagulation and a few drops of mercury to aid in the mixing of the blood as the syringe was rotated. The analyses were started as soon as a sample was obtained, and the blood was kept packed in ice until duplicate analyses had been made.

The pH of the blood was determined with a Cambridge glass electrode pH meter. The apparatus was calibrated with standard buffer solution before each determination. Duplicate determinations were made on each specimen, and checks to 0.02 unit were required. Oxygen content, oxygen capacity, and carbon dioxide content of whole blood were determined by the method of Van Slyke and Neill,[9] modified to compensate for the presence of small amounts ot ether, as described by Goldstein, *et al.*[5] The carbon dioxide content of the plasma was then read from the nomogram of Van Slyke and Sendroy[10] in volumes per 100 and converted to millimoles per liter by dividing by 2.226. The partial pressure of carbon dioxide (pCO_2) was then read from the nomogram of Van Slyke and Sendroy using the calculated value of the total plasma CO_2 in mM./L., [Total CO_2]p, and the observed pH. This nomogram is constructed from the Henderson-Hasselbalch equation:

$$pH = 6.10 + \log \frac{[\text{Total } CO_2]p - 0.0301 \quad pCO_2}{0.0301 \ pCO_2}$$

In those instances where the values were such that they could not be read on the nomogram, the pCO_2 was calculated directly from the Henderson-Hasselbalch equation. The bicarbonate value of the plasma, $[HCO_3]p$, is equal to the [Total CO_2]p minus the CO_2 dissolved in the plasma. The CO_2 dissolved in the plasma is equal to 0.0301 pCO_2. The bicarbonate value, $[HCO_3]p$, may thus be calculated from the equation:

$$[HCO_3]p = [\text{Total } CO_2]p - 0.0301 \ pCO_2$$

An increase or decrease in fixed acid in the blood can be determined by the difference in the bicarbonate value of the blood specimens at a standard pH of 7.4. In order to correct for the difference in the observed bicarbonate reading and the standard reading at 7.4, the buffer value of the blood must be known. Buffer value of a solution is defined as the amount of acid which must be added to cause a change of one pH unit. In plasma separated from red cells, the buffer value can be measured by the change in bicarbonate concentration when it is titrated with carbon dioxide and the buffer value can be calculated by dividing the change in bicarbonate by the change in pH. This value in normal plasma alone has been found to be about 8.6. However, in the presence of red cells an additional buffering effect is noted, and this has been found to be about 2.3 x (Hb expressed in mM./L.). Hb in millimoles per liter can be calculated from the oxygen capacity:

$$\frac{O_2 \text{ Capacity}}{1.34} = \text{Hb in Gm./100 cc.}$$

16.7 Gm. of Hb per liter = 1 mM. hemoglobin

Therefore:

$$\text{Hb mM./L.} = \frac{\text{Hb in Gm. per 100 cc. x 10}}{16.7}$$

The buffer value (β) of the blood can then be calculated from the equation:

$$\beta = 8.6 + 2.3 \text{ (Hb expressed in mM./L.)}$$

The value of the bicarbonate at pH 7.4 may be calculated by:

$$[HCO_3]p \text{ cor.} = [HCO_3]p + \beta \text{ (observed pH} - 7.4)$$

RESULTS

The results of this study of arterial blood in operations on 53 patients with an open thorax have been grouped in nine tables and are described under three headings: the oxygen saturation, the carbon dioxide tension and pH, and the change in concentration of fixed acids.

Oxygen Saturation. The ease with which the saturation of arterial blood with oxygen can be achieved during the course of an operation with an open thorax is illustrated in the first three tables. Table I presents this data in 13 pneumonectomies, Table II in nine lobectomies, and Table III in 16 miscellaneous operations with an open thorax in patients without significant pulmonary disease.

There was a mild degree of unsaturation of the arterial blood with oxygen before general anesthesia was induced in all three groups of patients. The average preoperative saturation was very similar in the three groups, 88.4 per cent in the pneumonectomies, 89.3 per cent in the lobectomies, and 88.9 per cent in the miscellaneous group. The cause for this moderate reduction in oxygen saturation is not obvious. It seems unlikely that it was due to pathologic changes in the lungs, because such pulmonary changes were not present in the third group (Table III) yet the degree of unsaturation was very similar. This preoperative reduction in arterial oxygen saturation may have been due to depression of respiratory activity by the preoperative medication.

Tables I, II, and III also list the arterial oxygen saturation in the three groups of patients some time after the induction of general anesthesia, and again toward the end of the operation. It can be seen that in these 38 patients, with three exceptions, there was a marked rise in the average oxygen saturation above the preoperative level after general anesthesia was induced. Patients L5, L6, and M9 showed a decrease in saturation. In the two latter, the decrease was certainly not large enough to be significant. In the great majority of patients a normal, or above normal, saturation was attained. In the 13 pneumonectomies, the average saturation was 97.5 per cent, in the nine lobectomies 96.3 per cent, and in the miscellaneous group 98.5 per cent. Some of the figures during operation referred to above were obtained before the pleura was opened, and some afterwards. The figures shown in Table VII, however, illustrate that the rise occurs with natural breathing in the lateral position before the start of controlled respiration with mechanical ventilation. Furthermore, in many of these patients, readings of the arterial saturation were also made with the Millikan oximeter. All such readings showed a rapid increase in the saturation of arterial blood with oxygen as soon as general anesthesia

with oxygen and ether vapor had been established. The rise in saturation, therefore, was undoubtedly due to the increased alveolar oxygen tension.

The average oxygen saturation towards the end of the operation was slightly lower, as shown in the next to the last columns in Tables I, II, and III.

TABLE I.—*Arterial Blood Saturation with Oxygen in Patients Before and During Pneumonectomy.*

Case Number	Before Operation	During Operation	Time After Start of Operation	During Operation	Time After Start of Operation
	Per Cent Saturation	Per Cent Saturation	Hours : Minutes	Per Cent Saturation	Hours : Minutes
P1	89.2	100.0	2:30	100.0	5:00
P2	84.0	....	....	92.4	3:00
P3	94.8	100.0	1:30	100.0	3:40
P4	88.9	99.3	2:12	98.9	4:15
P5	89.0	90.5	1:12	94.0	2:25
P6	89.2	99.0	2:00	97.1	3:15
P7	88.9	100.0	1:12	98.4	2:00
P8	90.3	....	....	98.7	2:00
P9	83.6	96.6	1:30	97.2	2:00
P10	83.8	96.1	1:15	82.3	4:15
P11	90.3	97.9	0:46	97.6	4:05
P12	86.5	96.8	1:10	92.6	3:40
P13	91.3	100.0	0:42	92.3	4:10
Average	88.4	97.5	1:27	95.5	3:22

This slight decrease in the average figures can probably be attributed to technical difficulties encountered in a few patients, *e.g.*, P10, L6, and M17.

There was a consistent decrease in the postoperative saturation of the arterial blood with oxygen in the 11 patients in whom this determination was

TABLE II.—*Arterial Blood Saturation with Oxygen in Patients Before and During Lobectomy.*

Case Number	Before Operation	During Operation	Time After Start of Operation	During Operation	Time After Start of Operation
	Per Cent Saturation	Per Cent Saturation	Hours : Minutes	Per Cent Saturation	Hours : Minutes
L1	84.8	87.0	2:00	87.2	2:00
L2	93.6	100.0	2:30	100.0	4:00
L3	89.4	92.0	2:00	92.3	4:00
L4	83.5	100.0	2:00	100.0	3:00
L5	91.3	87.0	2:00	88.5	5:00
L6	90.9	90.5	2:00	82.0	2:30
L7	84.8	100.0	1:12	100.0	3:45
L8	94.2	100.0	1:10	100.0	4:15
L	91.4	100.0	1:12	99.0	3:45
Average	89.3	96.3	1:27	94.3	3:35

made (Table VIII). The postoperative samples were obtained approximately two hours after operation with the patients in bed in an oxygen tent. The degree of oxygen saturation was very similar to that before operation. The decrease from the operative figures can be attributed to the fact that the gas

mixture in the oxygen tent had a much lower percentage of oxygen than that in the closed anesthetic circuit.

Carbon Dioxide Tension and pH. The removal of carbon dioxide from the blood during operation could not be achieved with the same success as the introduction of oxygen. This fact is illustrated in Tables IV, V, and VI, which also show the changes in pH which occur in conjunction with the changes in carbon dioxide tension. The patients have been grouped under the same headings as in Tables I, II, and III. Table IV gives the data on the same 13 pneumonectomies, Table V gives the data on the same nine lobectomies, whereas Table VI includes a larger group of miscellaneous operations with an open thorax, some of whom had pathologic changes in the lungs, such as inoperable cancer of the lung, fibroid tuberculosis, or marked degrees of emphysema. The data in three patients, M27, M28, and M29, shown in Table

TABLE III.—*Arterial Blood Saturation with Oxygen in Patients Without Pulmonary Disease, Before and During Thoracic and Thoraco-abdominal Operations.*

Case Number	Before Operation	During Operation	Time After Start of Operation	During Operation	Time After Start of Operation
	Per Cent Saturation	Per Cent Saturation	Hours : Minutes	Per Cent Saturation	Hours : Minutes
M1	87.4	98.3	3:00	91.4	5:00
M3	84.9	98.7	4:00	100.0	6:00
M5	88.2	....	....	99.3	1:30
M6	86.7	100.0	4:00	100.0	6:00
M7	91.3	....	....	100.0	3:00
M9	91.2	90.0	2:00	93.6	4:00
M10	90.7	100.0	3:00	102.0	5:00
M11	86.7	97.0	2:00	9 .5	4:00
M14	89.7	....	....	100.0	2:00
M15	89.3	98.3	2:00	95.7	3:00
M17	87.9	100.0	2:00	86.9	4:30
M24	94.4	99.8	1:30	99.0	3:06
M25	89.7	97 3	1:10	100.0	5:42
M27	88.6	100.0	0: 5	93.4	3:25
M28	89.3	100.0	0:42	....	....
M29	92.2	96.9	1:20	100.0	6:30
Average	88.9	98.5	2:07	95.6	4:11

III, are omitted in Table VI because of failure to obtain determinations of carbon dioxide, or pH, or both.

The average preoperative value of carbon dioxide tension was similar in all three groups. The median value was slightly higher in the group of 13 pneumonectomies than in the other two groups. The median preoperative value for pH was 7.38 in all three groups and the average value was essentially the same. Thus the preoperative median and average values for pH in these 48 patients were within normal limits, whereas the same values for carbon dioxide were very slightly above normal.

During the course of the operation, there was a tendency for the carbon dioxide tension to rise and the pH to fall. This tendency was most marked in

the pneumonectomies, less marked in the lobectomies, and least in the miscellaneous group. In the pneumonectomies, the average rise in the pCO_2 was 29 mm. Hg., with an increase of 18 mm. Hg. in the median value. The average increase in pCO_2 in the lobectomies was 21 mm. Hg., with an increase in

TABLE IV.—*Pneumonectomy. pH and pCO_2 of Arterial Blood Before and Near Completion of Operation.*

Case Number	pH		pCO_2 mm. Hg		Time After Start of Operation
	Before Operation	Near End of Operation	Before Operation	Near End of Operation	Hours : Minutes
P1	7.40	7.37	47	54	5:00
P2	7.39	7.38	42	59	3:00
P3	7.44	7.28	35	55	3:40
P4	7.34	7.15	47	74	4:15
P5	7.35	6.99	48	115	2:25
P6	7.47	7.11	36	91	3:15
P7	7.40	7.02	44	124	2:00
P8	7.38	7.31	47	52	2:00
P9	7.36	7.29	47	57	2:00
P10	7.35	7.25	50	64	4:15
P11	7.38	7.37	44	43	4:05
P12	7.39	7.17	46	97	3:40
P13	7.37	7.18	46	75	4:10
Average	7.39	.22	45	74	3:22
Median	7.38	7.25	46	64	3:40

the median value of 17 mm. Hg. In the miscellaneous group, the average rise was 13 mm. Hg., while the median rise was only 10 mm. Hg. The average fall in pH in the group of pneumonectomies was 0.17 with a fall in the median value of 0.13. In the lobectomies, the average fall in pH was 0.12, with a

TABLE V.—*Lobectomy. pH and pCO_2 of Arterial Blood Before and Near Completion of Operation.*

Case Number	pH		pCO_2 mm. Hg		Time After Start of Operation
	Before Operation	Near End of Operation	Before Operation	Near End of Operation	Hours : Minutes
L1	7.38	7.29	42	60	2:00
L2	7.32	7.43	50	40	4:00
L3	7.38	7.12	45	90	4:00
L4	7.41	7.17	43	86	3:00
L5	7.39	7.10	43	115	5:00
L6	7.35	7.20	39	62	2:30
L7	7.39	7.34	43	44	3:45
L8	7.37	7.29	42	47	4:15
L9	7.38	7.34	46	45	3:40
Average	7.37	7.25	44	65	3:34
Median	7.38	7.29	43	60	3:45

decrease in the median value of only 0.09. The miscellaneous group were quite similar to the lobectomies, with an average decrease of 0.12, and a decrease in the median value of 0.06. It is believed that the reference to average and median values is justified by the number of determinations which were made.

There were, of course, instances in which the ventilation was grossly inadequate, *e.g.*, P5, P7, L5, and M17. On the other hand, there were examples even in the pneumonectomy group, *e.g.*, P11, where the carbon dioxide tension was maintained at its preoperative value, or even lower. Similarly, there were several instances in which the pH fell to seriously low levels: P5, P7, and M17. In other instances, the pH was maintained at, or above, the preoperative level, *e.g.*, P2, P11, L2 and M10.

That the lateral position in itself was not responsible for the increase in carbon dioxide tension and the decrease in pH appears evident from the data

TABLE VI.—*Miscellaneous Operations with Open Thorax pH and pCO_2 of Arterial Blood Before and Near Completion of Operation.*

Case Number	pH		pCO_2 mm. Hg.		Time After Start of Operation
	Before Operation	Near End of Operation	Before Operation	Near End of Operation	Hours : Minutes
M1	7.44	7.34	34	46	5:00
M2	7.41	7.34	41	46	2:00
M3	7.40	7.34	42	46	6:00
M4	7.40	7.19	42	68	1:30
M5	7.42	7.36	43	49	1:30
M6	7.33	7.19	50	77	6:00
M7	7.38	7.33	43	49	3:00
M8	7.37	7.22	43	65	3:00
M9	7.41	7.14	42	90	4:00
M10	7.35	7.43	50	34	5:00
M11	7.48	7.20	45	95	4:00
M12	7.33	7.15	56	89	2:00
M13	7.51	7.32	31	51	2:30
M14	7.37	7.32	37	42	2:00
M15	7.40	7.38	40	42	3:00
M16	7.44	7.34	41	52	1:00
M17	7.37	6.94	40	134	4:30
M18	7.33	7.20	54	74	3:00
M19	7.29	7.19	60	68	3:15
M20	7.38	7.33	50	52	2:30
M21	7.29	7.13	54	75	3:09
M22	7.38	7.23	45	65	2:25
M23	7.39	7.37	39	42	4:00
M24	7.42	7.34	36	41	3:06
M25	7.31	7.30	52	44	5:42
M26	7.39	7.22	35	56	3:35
Average	7.38	7.26	44	57	3:20
Median	7.38	7.32	42	52	3:00

presented in Table VII. In this table, the preoperative values of pCO_2 and pH are compared with those made on samples obtained just before opening the pleura, approximately one hour after the start of the operation. Figures were obtained in four pneumonectomies, one lobectomy, and 12 miscellaneous operations. There was no change in the average value of pCO_2, and an increase in the median value of only 1 mm. Hg. In one instance, M22, there was an increase in pCO_2 of 20 mm. Hg. Thus, although inadequate ventilation may occur in the lateral position, it is not a consistent finding. The pH showed an average decrease of 0.06, with a decrease in the median value of 0.09. Com-

pared with the figures in Tables IV, V, and VI, these changes cannot be regarded as particularly significant. It seems obvious that the changes in carbon dioxide tension and pH during the course of the operation were largely a result of the open thorax, and not the lateral position upon the operating table.

In 11 patients, arterial blood samples were obtained approximately two hours after the end of the operation, when the patient was in bed in an oxygen tent. Two of these patients had pneumonectomies, two lobectomies, and seven had miscellaneous operations. Table VIII shows a comparison between the

TABLE VII.—*Effect of Lateral Position Before Opening Pleura—Respiration Not Assisted.*

	Arterial Blood						
	pH		pCO_2 mm. Hg.		Oxygen Saturation Per Cent		Time After Start of Operation
Case Number	Before Operation	Before Opening Pleura	Before Operation	Before Opening Pleura	Before Operation	Before Opening Pleura	Hours : Minutes
P10	7.35	7.36	50	41	84	96	1:15
P11	7.38	7.43	44	32	90	98	0:46
P12	7.39	7.32	46	47	87	97	1:10
P13	7.37	7.32	46	50	91	100	0:42
L8	7.37	7.28	42	46	94	100	1:10
M19	7.29	7.17	60	77	82	86	0:55
M20	7.38	7.39	50	47	83	96	1:00
M21	7.29	7.22	54	47	77	97	0:40
M22	7.38	7.21	45	65	84	94	0:45
M23	7.39	7.26	39	57	86	89	1:10
M25	7.31	7.24	52	60	90	97	1:10
M26	7.39	7.23	35	48	87	91	1:10
M27	7.34	7.27	49	51	89	100	0:55
M28	7.40	7.39	43	39	89	100	0:42
M29	7.31	7.37	52	42	92	97	1:20
M30	7.44	7.37	34	32	89	97	1:00
M31	7.36	7.25	46	51	89	100	1:00
Average	7.36	7.30	49	49	87	96	0:59
Median	7.37	7.28	46	47	89	97	1:00

values for carbon dioxide tension and pH before, during, and after operation on these patients. The average and median values for pCO_2 were lower, and for pH slightly higher, than those obtained near the end of the operation. The average pCO_2 was still 5 mm. Hg. above its preoperative value, and the average pH was 0.06 below the preoperative value. In general, where the respiratory acidosis was most marked near the end of the operation (P12 and M21) return towards normal, or preoperative values, was most marked. As stated above, the oxygen saturation decreased in the postoperative period below that present near the end of the operation.

Fixed Acids. The change in the concentration of fixed acids in the arterial blood was calculated in the group which showed the most severe respiratory acidosis, *i.e.*, the 13 pneumonectomies. Table IX presents the data on the case with the least respiratory acidosis, P11, the case with the greatest respiratory

acidosis, P7, and the average values for the group as a whole. As can be seen in the table, the average increase in fixed acids for the group as a whole near the end of the operation was only 2.7 millimoles per liter.

TABLE VIII.—*pH, pCO_2 and Oxygen Saturation of Arterial Blood Before Operation, Near End of Operation and Postoperatively.*

Case Number	pH			pCO_2 in mm. Hg.			Oxygen Saturation Per Cent			Postoperative Blood Sample
	Before Operation	Near End of Operation	Post-Operative	Before Operation	Near End of Operation	Post-Operative	Before Operation	Near End of Operation	Post-Operative	Time After End of Operation Hours:Minutes
P11	7.38	7.37	7.37	44	43	45	90	98	92	1:45
P12	7.39	7.17	7.31	46	97	45	87	93	85	1:35
L8	7.37	7.29	7.32	42	47	49	94	100	97	2:10
L9	7.38	7.34	7.34	46	45	48	91	99	92	2:10
M19	7.29	7.19	7.23	60	68	62	82	88	86	1:45
M20	.38	7.33	7.28	50	52	60	83	93	78	1:50
M21	7.29	7.13	7.29	54	75	52	77	85	82	1:55
M22	7.38	7.23	7.20	45	65	63	84	60	68	1:50
M23	7.39	7.37	7.39	39	42	39	86	89	82	2:00
M24	7.42	7.34	7.35	36	41	37	94	99	85	1:30
M26	7 39	7.22	7.31	35	56	48	87	93	89	2:25
Average	7.37	7.27	7.31	45	57	50	87	90	85	1:54
Median	7.38	7.29	7.31	45	52	48	86	93	85	1:50

TABLE IX.—*Change in Fixed Acid of Arterial Blood During Pneumonectomy-mechanical Respiration—Lateral Position.*

Blood Plasma	Case P11 with Minimum Respiratory Acidosis		Case P7 with Maximum Respiratory Acidosis		Average 13 Patients	
	Before Operation	Near End of Operation	Before Operation	Near End of Operation	Before Operation	Near End of Operation
pH B	7.38	7.37	7.40	7.02	7.39	7.22
pCO_2 mm. Hg B	44.0	43.0	44.0	124.0	45.0	74.0
Total CO_2 mM/L P	26.3	23.8	27.0	34.0	26.0	28.8
HCO_3 mM/L P	25.0	22.5	25.7	30.3	24.6	26.6
Hb gm. per cent B	14.4	13.3	11.2	12.8	13.9	14.0
Hb mM/L B	8.6	8.0	6.7	7.7	8.3	8.4
Buffer value β	28.4	27.0	24.0	26.3	27.7	27.9
Correction for pH mM/L	−0.6	−0.8	0.0	−10.0	−0.3	−5.0
HCO_3 Corrected mM/L p	24.4	21.7	25.7	20.3	24.3	21.6
Change in fixed acid mM/L	....	+2.7	....	+5.4	....	+2.7

DISCUSSION

With the method of anesthesia employed, there was no difficulty in maintaining adequate oxygenation during the course of long operations with an open thorax. Indeed the saturation of arterial blood with oxygen was higher during the operative procedure than it was in either the preoperative or the postoperative state. The increase in saturation occurred with the patients in the lateral position with unassisted respiration before opening the pleura. Oximeter readings indicated that the rise in saturation occurred promptly

with induction of general anesthesia with ether vapor and oxygen. It appears reasonable, therefore, to attribute this satisfactory degree of oxygenation during the operation to the increased oxygen tension in the alveolar air which follows the breathing of an anesthetic mixture rich in oxygen.

The average preoperative saturation of arterial blood with oxygen was somewhat below normal. As the condition was present even when there was no significant pulmonary disease (Table III), it may have been due to the preoperative medication. The average postoperative oxygen saturation was below normal and very similar to the preoperative saturation. As all the postoperative arterial blood samples were taken with the patient in an oxygen tent with an unobstructed airway, it would appear advisable to provide a higher content of oxygen than that afforded by the ordinary inefficient oxygen tent.

In all the patients reported here there was a tendency toward the development of respiratory acidosis during the course of the operation with an open thorax. The tendency was most marked in the group of pneumonectomies, less marked in the group of lobectomies, and least obvious in the group of miscellaneous operations. The respiratory acidosis was indicated by an increase in the carbon dioxide tension of the arterial blood, and was associated with a decrease in the pH. That there was no significant associated metabolic acidosis is evident from calculation of the change in concentration of the fixed acids in the group of pneumonectomies, the group showing the most marked respiratory acidosis. In our group of 13 pneumonectomies the average increase in fixed acids was 2.7 millimoles per liter, a figure which lies within the normal daily variation. Beecher,[1] in a similar calculation, noted an average increase in the fixed acids in six pneumonectomies of 9.3 millimoles per liter. The increase was less marked in the lobectomies and least marked in the miscellaneous operations in his series. Beecher suggested that possibly the high tension of carbon dioxide encountered in his series might interfere with cellular oxidation to the extent that the fixed acids accumulate. This explanation may well be valid, as in our series of pneumonectomies with mechanical ventilation of the lungs, the increase in the carbon dioxide tension was less than half that reported by Beecher in pneumonectomies with unassisted respiration.

The acidosis is then clearly respiratory and is due to the increased carbon dioxide tension in the alveolar air resulting from inadequate pulmonary ventilation. Beecher[2] has shown that the carbon dioxide tension does not rise in operations on patients in the supine position with a closed thorax, under ether oxygen anesthesia with an intratracheal tube. Ether is therefore apparently not a factor in the acidosis and pulmonary ventilation is adequate under these conditions. We also have found that under the same conditions, with the exception that the patient was in the lateral and not the supine position, the pulmonary ventilation was adequate and that there was no significant increase in the carbon dioxide tension of the arterial blood (Table VII). On the other hand, Beecher[1] observed respiratory acidosis with patients in the lateral position and the diseased lung uppermost. In these patients, however, the

lateral position was modified by placing a blanket roll or pillow, approximately five inches in diameter, beneath the thorax, placing the operating table in about five degrees Trendelenberg position, and breaking the table ten to 15 degrees at the head, and five degrees at the foot. Under these circumstances, ten of the 11 patients studied showed an average increase of 14.6 mm. Hg. in the carbon dioxide tension of the arterial blood. In the 17 patients whom we studied in the lateral position before opening the pleura, there was no increase in the average carbon dioxide tension. In some of these patients, *e.g.*, M25, M27, M28, and M29, there was no significant disease of the uppermost lung. Yet, even in the four pneumonectomies and one lobectomy in Table VII, there was no significant increase in carbon dioxide tension. The modified lateral position used by Beecher may be responsible for the difference in results. There can be no doubt that the lateral position interferes with the outward and cephalic movement of the ribs on the lower side of the thorax. It seems equally obvious that the placing of a roll or pad beneath the thorax, placing the operating table in a slightly head-down position and angulating the table beneath the thorax, would tend to produce further interference with the ventilation of the lower lung. We have not found such curvature of the thorax essential for good operative exposure and consequently have not employed it.

With one pleural cavity widely opened and no pleural adhesions, the respiratory muscles immediately become ineffective in the movement of gases in and out of the lungs. Under these circumstances, the lung fails to expand when the diaphragm moves downward and the ribs move outward. This is not only true on the side of the opened pleura, but also to a greater or lesser extent on the side of the unopened pleura, because the mediastinum moves to this side with inspiration, resulting in only partial expansion of the lower lung. It is thus obvious that pulmonary ventilation, solely dependent upon the action of the respiratory muscles, in the presence of an open thorax will be markedly impaired. The degree of impairment of pulmonary ventilation will be dependent upon a number of factors, such as the presence or absence of adhesions to the chest wall or diaphragm, the degree of mobility of the mediastinum, the presence or absence of an opening in the opposite pleural cavity and whether or not the position on the operating table contributes to the interference with inflation and deflation of the lung.

The presence of a severe acidosis at the conclusion of a long operation with an open thorax is certainly undesirable, and may contribute to some of the hitherto unexplained fatalities which occur. Unfortunately, we do not have data on a control series of patients with unassisted respiration. Beecher,[1] however, has reported such a series. The degree of respiratory acidosis which he reported in five pneumonectomies was approximately twice as great as in the 13 pneumonectomies reported here in whom mechanical ventilation was used. Again, the respiratory acidosis in the eight lobectomies reported by Beecher was approximately 50 per cent greater than in the nine lobectomies reported here. The five miscellaneous operations reported by Beecher showed

approximately the same degree of respiratory acidosis as the 26 miscellaneous operations reported here. More recently, Beecher[3] has reported similar studies on pneumonectomies and lobectomies with assisted respiration in the lateral position and with unassisted respiration in the Overholt prone position. The three pneumonectomies with assisted respiration showed approximately the same degree of acidosis as in the 13 pneumonectomies with mechanical respiration reported here. On the other hand, the ten lobectomies with assisted respiration showed no significant respiratory acidosis, in contrast to the nine lobectomies reported here with mechanical ventilation of the lungs, who showed an average increase in carbon dioxide tension of 21 mm. Hg. and an average decrease in pH of 0.12. Beecher also reported five pneumonectomies and four lobectomies in the prone position with unassisted respiration who exhibited no significant respiratory acidosis. The disparity between the number of cases referred to above as reported by Beecher and those published by him[1, 3] arises from the fact that we have only referred to those cases where determinations of pH and carbon dioxide tension were made preoperatively and near the end of operation.

Because of the small number of cases, the comparisons drawn between average figures in the preceding paragraph may not be valid. But the conclusion seems inescapable that in the lateral position, ventilation of the lungs is improved when normal breathing is augmented by manual compression of the rebreathing bag in the anesthetic circuit, or when ventilation of the lungs is completely taken over by mechanical means. At first glance, it would appear that the prone position with unassisted respiration is more successful in avoiding respiratory acidosis than the lateral position with either assisted respiration or mechanical ventilation. However, further studies must be done before such a conclusion is warranted. Furthermore, in the cases reported by Beecher there is a striking disparity between the preoperative pH values in the cases with unassisted respiration and the preoperative pH values of the cases in the prone position. The difference in these values in the pneumonectomies was 0.12 and in the lobectomies 0.16. The cases in the prone position in each instance showed the lower average preoperative value.

We have been unable to find any studies on respiratory acidosis during pnemonectomies, or other open thoracotomies, with patients in the supine position. The present authors are firmly convinced, however, that neither the supine nor prone positions afford the same advantageous exposure for the performance of a difficult pneumonectomy that the lateral position does. We feel, therefore, that a more strenuous effort should be made to improve the ventilation during the course of operations with an open thorax with the patient in the lateral position, rather than abandon a position which affords the best surgical exposure in favor of a position which improves ventilation.

We hold no particular brief for mechanical ventilation of the lungs over manual compression of the rebreathing bag. It is obvious that both can accomplish the same desired objective of improving pulmonary ventilation. On the

other hand, we can see no objection to mechanical ventilation, which has been used satisfactorily for many years in laboratory experiments on animals. It frees the anesthetist from the tiresome repetitive task of squeezing a rubber bag 14 to 16 times a minute. The rate and depth of ventilation are more uniform and can be more accurately controlled with a mechanical apparatus. We have used mechanical ventilation at the Jefferson Hospital for over two and a half years in all operations involving an open thorax with complete satisfaction. Such apparatuses do not involve any additional hazard of explosion, as no electric motor is necessary in the operating theatre. Any source of compressed air is suitable, either piped into the operating room, taken from tanks, or drawn from a rubber hose leading from a small electric air-compressor in an adjoining room.

Finally, whatever method of pulmonary ventilation, or whatever position is used in operations with an open thorax, there is always the possibility that an occasional patient may develop severe respiratory acidosis. We know of no clinical signs or symptoms which can be depended upon to recognize such acidosis. Unfortunately, an increase in carbon dioxide tension, or a decrease in pH, produces no color change in the skin and mucous membranes such as results from a decrease in the saturation of hemoglobin with oxygen. The intermittent sampling of arterial blood is troublesome and time-consuming. It is to be hoped therefore that some method of continuous, or intermittent and rapid, determination of the carbon dioxide content of expired air may be developed. Such a method will enable the anesthetist and the surgeon to recognize the development of respiratory acidosis and to take steps to correct this serious and often unrecognized condition.

SUMMARY

1. A clinical study of the respiratory gas exchange has been made during the course of 53 operations involving an open thoracotomy. These operations comprised 13 pneumonectomies, nine lobectomies and 31 miscellaneous operations. All patients were operated upon in the lateral position. While the pleura was open, curare was administered and pulmonary ventilation was maintained by mechanical insufflation. Samples of arterial blood were drawn preoperatively, before opening the pleura, toward the end of the operation, and approximately two hours postoperatively. The blood samples were analyzed for oxygen content and capacity, carbon dioxide content, and pH. From these determinations, the carbon dioxide tension and, in the pneumonectomies, the change in concentration of the fixed acids were calculated.

2. Satisfactory oxygenation was maintained throughout the operative period, whereas the preoperative and postoperative levels of oxygenation were both somewhat below normal.

3. There was a tendency towards the development of respiratory acidosis during the course of these operations. This tendency was most marked in the pneumonectomies, less marked in the lobectomies, and least obvious in the group of miscellaneous operations.

4. In the group of pneumonectomies, in which respiratory acidosis was most marked, there was no significant associated metabolic acidosis.

CONCLUSIONS

Respiratory acidosis may occur in any operation involving an open thorax. The acidosis is a result of inadequate pulmonary ventilation. With the patient in the lateral position ventilation should be manually assisted, or taken over by mechanical means. The development of a practical method for the early detection of respiratory acidosis constitutes a challenge to those interested in the future development of this field of surgery.

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DISCUSSION.—DR. JOHN H. GIBBON, JR.: We do not mean to imply by this study that mechanical insufflation is the only method of insuring adequate pulmonary ventilation. However, in our hands it has been of great help.

We do wish to emphasize that you cannot regard the patient's condition as good merely because he is not cyanotic. In all of the patients reported here there was adequate saturation of the blood with oxygen. The lowering of the pH and the increase in the carbon dioxide tension of the blood does not produce any obvious signs or symptoms in a patient under anesthesia such as you would expect to find in an unanesthetized patient.

When the thorax is widely opened, the problem consists in being sure that the patient has adequate ventilation and exchange. Only in that way can you avoid respiratory acidosis, and I think for the present that a good bit of attention will have to be paid to the pH of the blood during prolonged operations with the thorax opened.

QUANTITATIVE STUDIES ON THE MECHANISM OF GASTRIC SECRETION IN HEALTH AND DISEASE*

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THE PURPOSE OF THE PRESENT INVESTIGATION has been to study by quantitative methods the relative importance of the mechanisms which stimulate gastric secretion in normal animals and in patients with various types of peptic ulcer. It has now been well established that an excessive secretion of gastric juice occurs in patients with duodenal ulcers, both in the fasting stomach and as a result of the stimulus of food. That this hypersecretion of gastric juice is significant in the pathogenesis of peptic ulcer is indicated by the finding, repeatedly confirmed, that if a hypersecretion of gastric juice is produced in experimental animals by continuous stimulation of the gastric glands by the method of Wangensteen and his associates,[1] typical peptic ulcers appear in the stomach and duodenum and display the characteristics of progression, chronicity, hemorrhage, and perforation seen in clinical lesions.

In the normal mechanism of gastric secretion, physiologists[2] have recognized a cephalic, or nervous, phase of secretion, a gastric phase, and an intestinal phase. These terms refer to the fact that gastric secretion may be stimulated by impulses in the secretory fibers of the vagus nerves aroused reflexly by the sight, odor, or taste of food, and that it may be also stimulated by the presence of food or certain food products in the stomach or in the intestines. The nervous mechanism of gastric secretion was extensively studied by Pavlov and his pupils[3] and its main features securely established. The manner in which food in the stomach and intestines produces stimulation of the gastric glands is less well understood. Furthermore, no information has been obtained concerning the relative importance of these three phases of stimulation so that it has not been possible to state what proportion of the total output of gastric juice is dependent on the nervous mechanism, and what is due to the gastric and intestinal phases respectively. Such data should be helpful to the surgeon, since it has become apparent that success in the surgical treatment of peptic ulcer is directly proportional to the degree to which the abnormality in gastric secretion present can be corrected.

The development in our laboratory of a method for the complete collection of gastric secretion from Pavlov and totally isolated stomach pouches for long

* This work has been aided by grants from the Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Service and the Otho S. A. Sprague Memorial Institute. Read before the American Surgical Association, Colorado Springs, Colo.

periods of time has made it possible to re-study the mechanisms of gastric secretion from the quantitative point of view. Instead of making an external fistula, a cannula of the type illustrated in Figure 1 is inserted into the cavity of the isolated pouch and the gastric wall infolded by several purse string sutures around the shaft. Omentum is wrapped around the cannula, which is then led through a stab wound in the abdominal wall. The carefully rounded flange prevents the cannula from traumatizing the mucosa and from pulling out of the pouch. A football bladder is attached to the cannula by a threaded metal adapter so that a closed method of collection is established. Animals provided with cannulae of this type have been kept in good condition for three to four years with practically no loss of secretion.

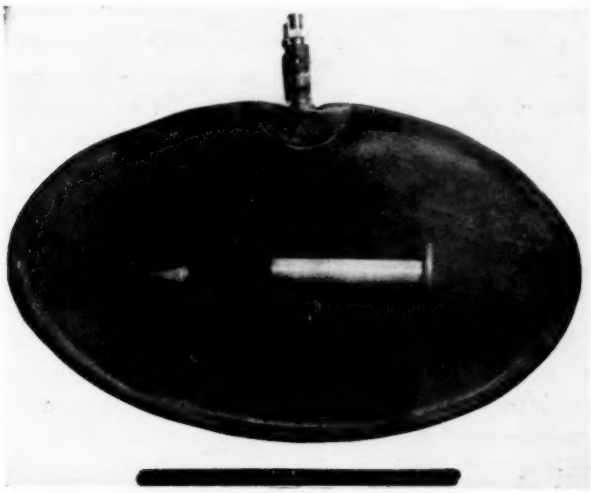


FIG. 1.—Photograph showing the nylon plastic gastric cannula, adapter, and football bladder used for the collection of gastric secretion.

QUANTITATIVE STUDIES ON THE CEPHALIC PHASE OF GASTRIC SECRETION

For this investigation, dogs were prepared with totally isolated stomach pouches of the type devised by Dragstedt and Ellis.[4] The vagus nerves and blood supply to the isolated stomach were carefully preserved. The esophagus was anastomosed to the end of the duodenum. Dogs prepared in this manner lose all of their gastric secretion via the cannula and become rapidly hypochloremic and dehydrated. They can be preserved in good condition by the daily intravenous injection or from one to two liters of physiologic salt solution. Food passes directly from the esophagus into the duodenum, and when the animal first begins to eat, there is usually considerable dysphagia. This gradually subsides as the animal learns to eat more slowly. The functional integrity of the vagus nerves is indicated by a marked secretion of gastric juice in the isolated stomach in response to insulin hypoglycemia.

After a control period of several weeks during which the animals were fed a standard diet, and the gastric secretion carefully collected, the vagus nerves were divided or crushed by a transthoracic operation and the observations repeated. Experiments of this type were performed on 12 animals, and the details have been reported elsewhere.[5] The results of a representative experiment are graphically illustrated in Figure 2. The gastric secretion is expressed in terms of milliequivalents of hydrochloric acid secreted by the isolated stomach in a 24-hour period. This is determined by multiplying the volume of juice collected in liters by the free acid expressed in terms of clinical units. In the 12 animals studied quantitatively in this manner, vagotomy produced a decrease in the volume of gastric juice secreted by an average of 56 per cent. The decrease in free acidity of the 24-hour secretion varied from 18 to 82 per cent, averaging 49 per cent. The reduction in the 24-hour output of hydrochloric acid varied from 46 to 92 per cent, averaging 76 per cent.

The persistent effect of vagotomy is illustrated in the chart in Figure 3, showing the results of crushing the vagus nerves above the diaphragm on the gastric secretion of dog D–962 provided with a total gastric pouch. A very profound reduction in the secretion of gastric juice was produced, and this persisted without significant alteration two years later. These findings are in harmony with the observations that we have made respecting the effect of vagotomy on the nocturnal secretion of gastric juice in patients with duodenal ulcer. In 19 patients with duodenal ulcers treated by vagotomy alone, the night secretion of gastric juice was markedly decreased and persisted at the low level for periods ranging from two to seven years.[6]

Quantitative studies of the effect of vagotomy on gastric secretion from the totally isolated stomach permit of a comparison between the nervous and intestinal phases of secretion only. Food passes in these animals directly from the esophagus into the duodenum, and consequently, the gastric phase of secretion is entirely absent. As will be seen in subsequent experiments, the antrum, while a part of the isolated stomach, is functionless as a stimulus for gastric secretion when it does not come in contact with food. These data therefore indicate that the nervous phase of gastric secretion is more important than the intestinal phase in the ratio of at least four to one.

QUANTITATIVE STUDIES ON THE GASTRIC AND INTESTINAL PHASE OF GASTRIC SECRETION

Pavlov and his pupils recognized that gastric secretion was stimulated by the presence of food in the stomach, or in the intestines, and that this secretion could be produced even after the vagus nerves to the stomach had been completely divided. These findings were subsequently confirmed by the experiments of Lim, Ivy, and McCarthy,[7] Ivy and Farrell,[8] and Webster and Armour.[9] The mechanism of this stimulation has been extensively studied. That a humoral factor is involved was firmly established by Ivy and Farrell[8]

FIG. 2

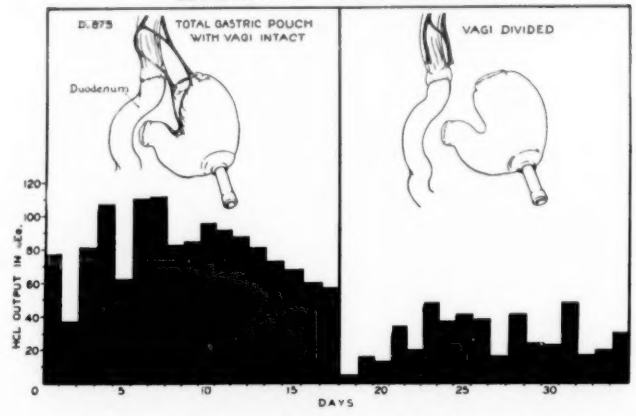
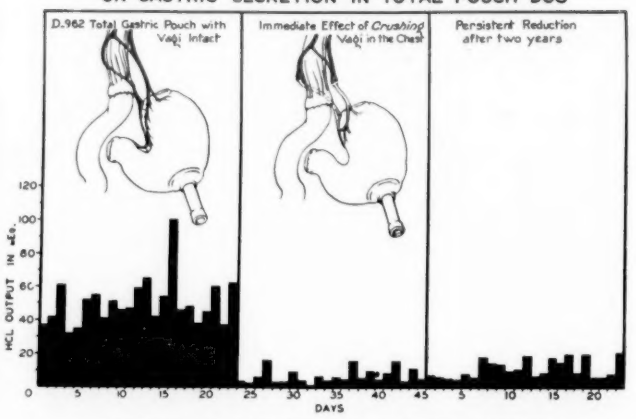


FIG. 3


IMMEDIATE AND REMOTE EFFECT OF VAGOTOMY ON GASTRIC SECRETION IN TOTAL POUCH DOG
D. 962 Total Gastric Pouch with Vagi Intact
Immediate Effect of Crushing Vagi in the Chest
Persistent Reduction after two years
HCL OUTPUT IN mEq.
DAYS

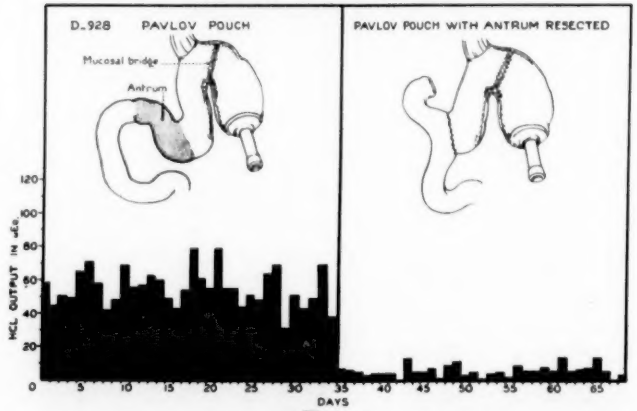

EFFECT OF RESECTION OF ANTRUM ON GASTRIC SECRETION IN PAVLOV POUCH
D. 928 PAVLOV POUCH
PAVLOV POUCH WITH ANTRUM RESECTED
Mucosal bridge
Antrum
HCL OUTPUT IN mEq.
DAYS

FIG. 4

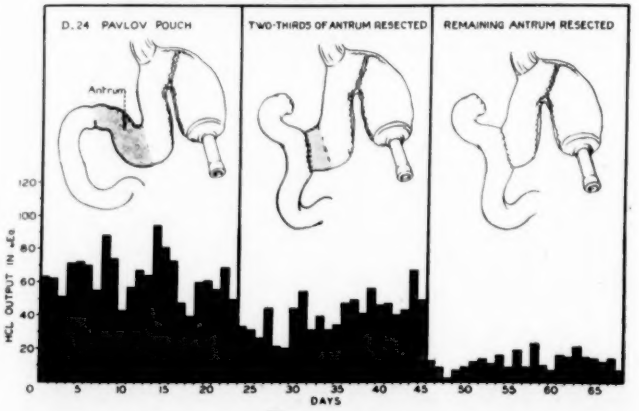

EFFECT OF PARTIAL REMOVAL OF ANTRUM ON GASTRIC SECRETION IN PAVLOV POUCH
D. 24 PAVLOV POUCH
TWO-THIRDS OF ANTRUM RESECTED
REMAINING ANTRUM RESECTED
Antrum
HCL OUTPUT IN mEq.
DAYS

FIG. 5

when they showed that a completely denervated fundic pouch transplanted into the mammary glands would secrete acid gastric juice in response to food taking.

As early as 1906, Edkins[10] reported that the intravenous administration of extracts of the mucous membrane of the antrum of the stomach stimulated gastric secretion, whereas similar extracts made from other parts of the stomach had little or no effect. In 1909, Edkins and Tweedy[11] reported that the secretion of acid by the fundus of the stomach could be stimulated by introducing various food substances into the antrum, which had been separated from the fundus by a diaphragm. As a result of these studies, and influenced, no doubt, by the recently discovered pancreatic secretin, Edkins postulated that this fundic secretion was due to a hormone, which he named "gastrin" and which was produced by the mucosa of the antrum in response to chemical stimulation by foodstuffs.

Uncertainty with respect to the validity of this gastrin hypothesis of Edkins has arisen among physiologists largely as a result of two main lines of work. Keeton, Koch, and Luckhardt[12] found that the gastric secretogogue in extracts of pyloric mucosa is not specific for this membrane, but may also be obtained from the duodenal mucosa, the liver, ileum, pancreas, and even the thyroid gland. It has been suggested that the stimulating substance in Edkins' early extracts was histamine. Ivy and Whitlow[13] put the gastrin theory to physiologic test by preparing animals with both a Pavlov pouch and with an isolated pouch of the antrum of the stomach as well. Even prolonged contact of the antrum mucosa with a wide variety of food substances failed to cause a stimulation of gastric secretion in the Pavlov pouch. In a similar type of experiment, Priestley and Mann[14] likewise reported no increase in the secretion of gastric juice as a result of stimulation of an isolated antrum pouch in dogs provided with a fundic fistula.

Data obtained from studies on the effect of excision of the antrum of the stomach on gastric secretion in experimental animals have also been conflicting. In 1923, Smidt[15] reported marked reduction in the secretion of gastric juice from a Pavlov pouch when the antrum was resected. Removal of the pylorus alone caused no effect on secretion, and antrum exclusion after the method of von Eiselsberg caused an actual increase in secretion. In a similar type of experiment, Portis and Portis[16] reported no change in the concentration of free hydrochloric acid in the juice from a Pavlov pouch following removal of the pyloric antrum. Thompson[17] reported no change in the acid concentration in the Pavlov pouch secretion after antrum resection, but noted that in normal dogs, resection of the antrum produced a progressive decrease in the acid concentration of the entire stomach content in response to a test meal. Wilhelmj and his associates[18] concluded that a lowering in the acidity of the gastric content of dogs following resection of the antrum was more than could be accounted for by neutralization and dilution, and that actual reduction in acid secretion was produced by this operation.

These various studies led to the view that whereas the secretion of gastric

juice, which resulted from the presence of food in the stomach or intestines of animals after complete vagotomy, was due to stimulation of the gastric glands by a humoral agent, this was believed to arise from the mucous membrane of the stomach and intestine and not specifically from the antrum. On the other hand, surgeons, who had noted the high incidence of marginal ulcer following gastrectomy in which the antrum was excluded by the method of Finsterer and Devine, came to regard the antrum mucosa as of special importance. In a number of such marginal ulcers, McKittrick, Moore, and Warren[19] reported that the ulcers healed following subsequent excision of the remaining antrum without additional treatment.

In a recent study in our laboratory,[20] Pavlov pouches were prepared in 11 dogs, and after a control period, during which the entire secretion from the pouch was collected quantitatively for several weeks, the antrum of the stomach was removed and the effect on secretion determined for a comparable time. The output of free hydrochloric acid by the Pavlov pouch was reduced by an average of 86 per cent, or to one-sixth of the control level. This reduction is apparently permanent. One animal has been observed for 24 months after the antrum removal, and the pouch secretion has remained at the low level. The effect is graphically illustrated in the charts in Figures 4 and 5. It is significant with respect to the physiology of the antrum that resection of one-half or even two-thirds, of the antrum has no effect on secretion, but that when the remnant is removed, the full depressant effect is seen.

This experiment, in addition to demonstrating the remarkable effect of the antrum on the secretion of gastric juice by the fundus of the stomach, provides an opportunity for comparing the relative importance of the gastric and intestinal phases of secretion. Although the experiment was performed with Pavlov pouches with some preservation of vagus innervation, we have learned that this is so meager as to have little or no influence on the total amount of juice produced by the isolated pouch. The nervous phase was thus either minimal or entirely absent. The antrum mechanism of secretion is thus more important than the intestinal phase by a ratio of six to one.

The discovery of the marked effect of complete antrum resection on gastric secretion from the Pavlov pouch suggested experiments of the type illustrated in Figure 6. After a control period of secretion, the stomach was divided between the antrum and fundus and the upper end of the antrum closed. The stump of stomach was then anastomosed to the side of the duodenum from eight to ten centimeters from the pylorus. To our surprise, exclusion of the antrum in the experiment illustrated in Figure 6 produced almost as great a reduction in secretion from the Pavlov pouch as was subsequently secured by excision of the antrum. Exclusion of the antrum in this manner was carried out on a number of other Pavlov pouch dogs, but no effect on secretion was produced. We attribute the marked reduction in secretion in this one case to the probability that food failed to regurgitate through the pylorus into the antrum, but that such regurgitation occurred in the other experiments and prevented a reduction in secretion by the Pavlov pouch.

The experiment illustrated, however, is of interest because when the anastomosis between the fundus of the stomach and the duodenum was disconnected, and the fundus re-anastomosed to the end of the antrum so that the original relationship was restored, the gastric secretion from the Pavlov pouch returned to the control level. When subsequently the antrum was resected, the secretion of gastric juice fell off to a level somewhat lower than that of the period of exclusion. This experiment demonstrates that interruption of the intrinsic nervous connections between the antrum and the main stomach does not interfere with antrum function.

Further information concerning the function of the antrum of the stomach was obtained by transplantation experiments of the type illustrated in Figure 7. A Pavlov pouch was prepared in the customary manner and the gastric secretion collected quantitatively for a control period. In dog D–172, the average output of hydrochloric acid from the pouch was about 70 milliequivalents per day. The antrum of the stomach was then exteriorized to eliminate completely contact with food, and the stump of fundus was anastomosed to the side of the duodenum. An immediate and persistent marked decrease in gastric secretion followed, showing that the antrum is functionless in this situation. The antrum was then transplanted into the side of the colon, where it formed a diverticulum. The original blood supply to the antrum was preserved. A marked and persistent hypersecretion of gastric juice from the Pavlov pouch resulted, which was much greater than during the control period when the antrum was in its normal location. This phenomenon has been repeatedly observed in other experiments in which the antrum of Pavlov pouch dogs, or from the totally isolated stomach, has been subsequently transplanted into various portions of the intestinal tract. The antrum has uniformly remained functionless when deprived of contact with the food in the alimentary tract. The excessive response of the stomach mucosa produced when the antrum is transplanted into the colon suggests that the alimentary content can stimulate the antral mucosa, even after most of the food substances have been previously absorbed. The hypersecretion produced when the antrum is in the colon suggests that either the reaction of the colon content, or its chemical composition, is a more effective stimulant to the antrum mucosa than is the normal content of the stomach.

The experiment with dog D–167, graphically presented in Figure 8, provides a comparison of the effect of antrum exteriorization and of antrum transplantation into the colon and into the duodenum. A totally isolated stomach pouch was prepared with the vagus innervation to the stomach divided, and the gastric secretion was collected for a control period of 17 days. The antrum was then carefully separated from the fundus without interfering with its blood supply and transplanted into the colon, where it formed a diverticulum. A tremendous augmentation in gastric secretion from the isolated fundus resulted and persisted for several weeks until the antrum was disconnected from the colon and exteriorized. The blood supply to the isolated antrum was not interfered with, but when it was removed from con-

FIG. 6

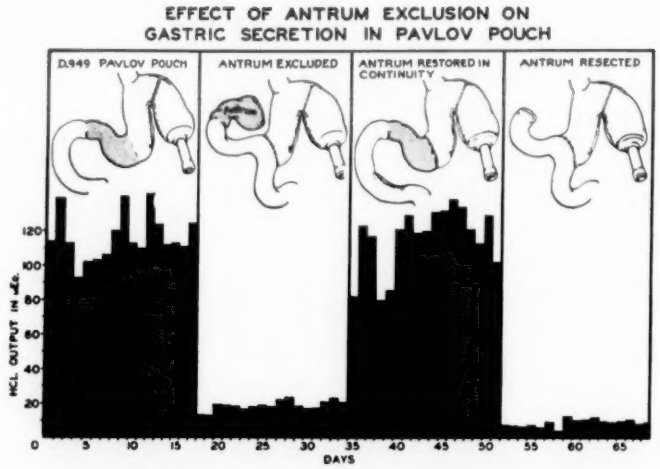
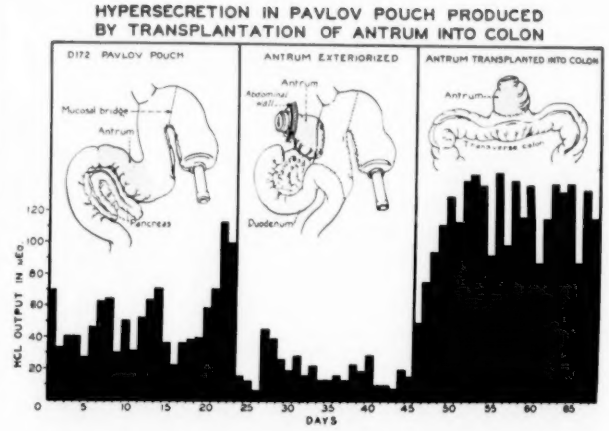


FIG. 7



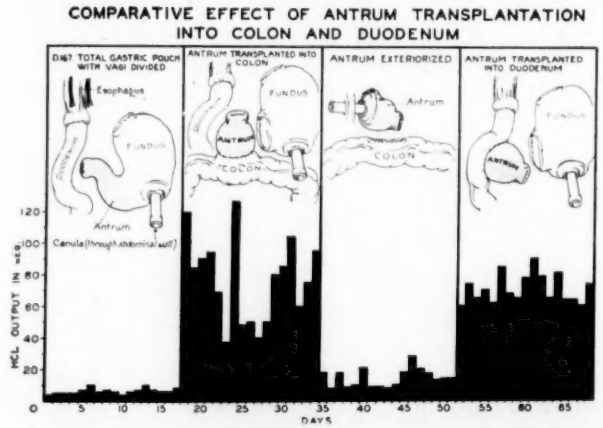


FIG. 8

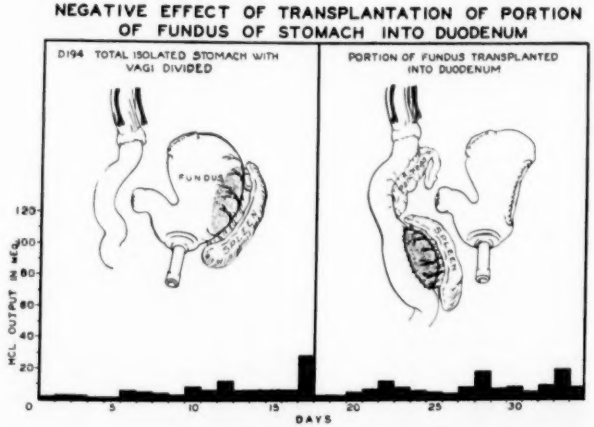

NEGATIVE EFFECT OF TRANSPLANTATION OF PORTION
OF FUNDUS OF STOMACH INTO DUODENUM
D194 TOTAL ISOLATED STOMACH WITH VAGI DIVIDED
PORTION OF FUNDUS TRANSPLANTED INTO DUODENUM
FUNDUS
HCL OUTPUT IN mEq.
DAYS

FIG. 9

tact with the intestinal content, the secretion of gastric juice in the isolated fundus fell off to the low level seen during the first control period. This finding, repeatedly confirmed, shows that the antrum is functionless when a part of the isolated stomach and exposed only to gastric secretion and mucus. On the other hand, when the mucosa of the antrum is exposed to the colon content, it produces a marked augmentation of gastric secretion. When subsequently the exteriorized antrum was implanted into the duodenum, an augmentation of gastric secretion was produced almost as great as when the antrum was implanted into the colon.

The striking effect secured by resection, exteriorization, and transplantation of the antrum proves that this part of the stomach has a specific and important function as the chief source, or possibly the only source, of the gastric secretory hormone, gastrin. A control experiment supporting this statement is shown in Figure 9. Dog D–194 was provided with a totally isolated stomach pouch with the vagus nerves divided. A meager secretion of gastric juice characteristic of this type of preparation was obtained, and its hydrochloric acid output determined. A portion of the fundus of the stomach along the greater curvature was excised and transplanted with the attached spleen as a diverticulum into the side of the duodenum. No effect on gastric secretion was produced. Since a transplantation of a segment of the antrum of similar size has been uniformly found to cause a tremendous augmentation in gastric secretion, it is evident that the mucosa of the fundus of the stomach does not elaborate the gastric secretory hormone.

An attempt was made to secure experimental data with respect to the relative importance of the three phases of gastric secretion in the experiment charted in Figure 10. An isolated pouch of the entire stomach with the vagus nerves intact was prepared in dog D–954. During the control period, the output of hydrochloric acid from the isolated stomach averaged 55 milliequivalents per 24-hour period. The nervous and intestinal phases of secretion only were present, since the antrum is functionless when a part of the isolated stomach. The vagus nerves were then divided, and the secretion of gastric juice fell off to an average hydrochloric acid output of 20 milliequivalents per day. Only the intestinal phase of secretion was operative during this period. The antrum was then disconnected from the isolated stomach and implanted in continuity in the second portion of the duodenum. Care was taken not to interfere with the original blood supply to the antrum or the stomach. The output of hydrochloric acid by the isolated fundus increased immediately to an average of 80 milliequivalents per day. During this period, the gastric and intestinal phases of secretion were present.

Similar experimental data with respect to the relative importance of the three phases of gastric secretion were obtained from studies on the two types of isolated stomach pouches illustrated in Figure 11. Of 11 animals studied in our laboratory where a vagus innervated, totally isolated stomach preparation has been made, and the esophagus anastomosed to the duodenum, an over-all average maximum of 973 cc. of gastric juice was produced in a 24-hour

period. Ten animals with this same type of preparation, but with the vagus nerves divided, secreted an average of 220 cc. of gastric juice per day. On the other hand, in ten animals prepared with a vagus innervated, totally isolated fundus, and with the esophagus anastomosed to the antrum, an average

FIG. 10

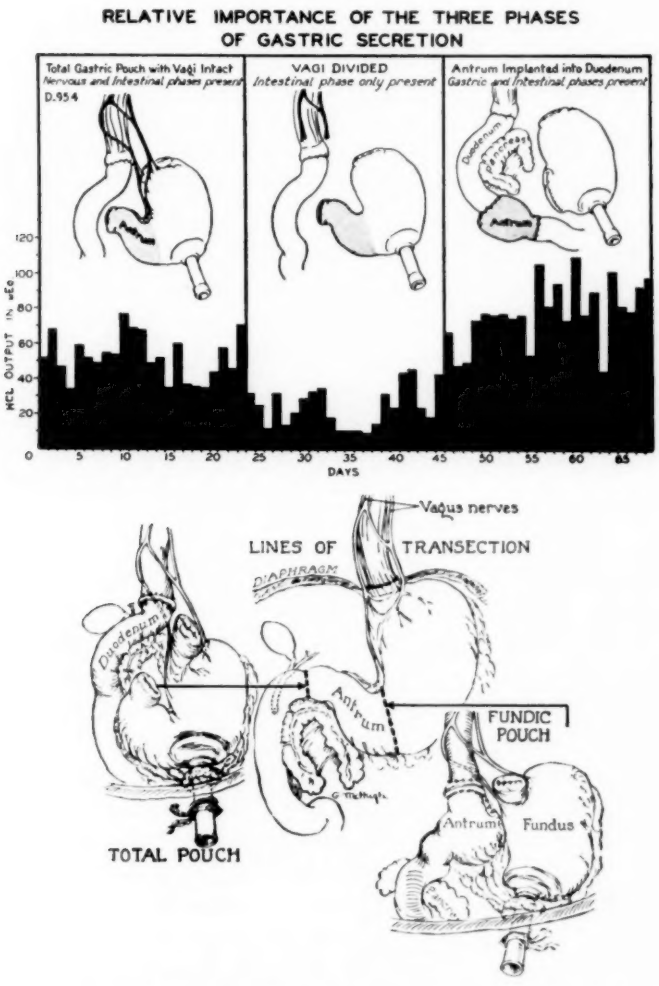


FIG. 11.—Diagrams illustrating the total stomach pouch in which the nervous and intestinal phases of secretion are present and the fundic pouch in which the nervous, antrum, and intestinal phases of secretion are present.

maximum secretion of 1687 cc. per 24 hours was secured. If we use the volume of gastric juice secreted as an index of the activity or relative importance of the phases of gastric secretion, it would then appear that in normal dogs, when the intestinal phase only is present, an average of 220

cc. of gastric juice per day is secreted. When both the intestinal phase and the nervous phase of secretion are operative, an average maximum of 973 cc. of gastric juice will be secreted. When, however, all three phases of secretion are present, an average maximum of 1687 cc. is produced per day. While there are, of course, many inaccuracies in an experimental analysis of this kind, it seems probable that the nervous and antrum phases of secretion account for 90 per cent of the gastric juice produced in a 24-hour period in normal animals, and the intestinal phase 10 per cent, or less.

THE GASTRIC SECRETION IN PEPTIC ULCER

While the older gastro-enterologists believed that most ulcer patients secreted more gastric juice in response to test meals than normal individuals,

TABLE I.—*Average Twelve-Hour Night Gastric Secretion in the Empty Stomach of Normal Individuals and Peptic Ulcer Patients.*

	Number of Cases	Volume cc.	Free Acid Clinical Units	HCl Output Milli-Equiv.
Normal	81	551	33	18
Duodenal ulcer	135	1,085	52	60
Duodenal ulcer after vagotomy	70	521	22	11
Gastric ulcer	14	773	23	17.8
Gastric ulcer after vagotomy	10	465	3	1.4

precise data concerning the abnormality in gastric secretion characteristic of ulcer patients has only been obtained recently with the adoption of quantitative methods for the collection of gastric juice over measured periods of time. Our own studies during the past eight years have been directed primarily toward a measurement of the continuous nocturnal secretion obtained by aspirating the gastric content by means of an indwelling nasal catheter attached to a Wangensteen-type suction apparatus. Data obtained on the 12-hour night gastric secretion in the empty stomach of normal individuals and of patients with duodenal and gastric ulcers is presented in Table I. Eighty-one normal people, or surgical patients without gastro-intestinal disease, were found to secrete an average of 18 milliequivalents of hydrochloric acid in the 12-hour night secretion, whereas when tested by the same method, 135 duodenal ulcer patients secreted 60 milliequivalents, or almost four times as much. In sharp contrast to this hypersecretion, found characteristic of duodenal ulcer patients, 14 patients with gastric ulcers secreted an average of 17.8 milliequivalents, or almost exactly the same as the normal individuals. These findings are in harmony with data reported from a number of recent clinics. The hypersecretion in duodenal ulcer patients in our experience has almost uniformly been abolished by complete vagotomy. In the 70 patients listed in Table I, the output of hydrochloric acid following vagotomy was 11 milliequivalents, which compares with 18 milliequivalents put out by normal individuals. The evidence is thus conclusive that in the great majority of

duodenal ulcer patients, the excessive continuous secretion in the empty stomach is of nervous origin and is presumably due to a secretory hypertonus in the vagus nerves.

That the gastric glands in duodenal ulcer patients will respond to hypoglycemia, produced by a standard dose of insulin, by a greater output of hydrochloric acid than occurs in normal individuals was demonstrated by Welin and Frisk[21] in 1936 and recently confirmed by Winkelstein, and also in our clinic. In an excellent study on human gastric secretion in 1939, Ihre[22] demonstrated that the fasting secretion of gastric juice in duodenal ulcer

TABLE II.—*Gastric Secretion in Health and Disease.*
(Calculated from data of Bengt Ihre)

			Fasting Secretion (60 min.)			Histamine Secretion[1] (60 min.)			Insulin Hypoglycemia[2] Secretion (60 min.)		
Subject	Sex		Vol. cc.	Free Acid cl. units	HCl Output m.eq.	Vol. cc.	Free Acid cl. units	HCl Output m.eq.	Vol. cc.	Free Acid cl. units	HCl Output m.eq.
Normal	Male	17	47	60	2.82	112	119	13.33	140	123	17.22
	Female	6	20	46	0.92	69	97	6.69	109	129	14.06
Duodenal	Male	10	96	60	5.76	178	85	14.83	193	92	17.76
ulcer	Female	5	94	70	6.58	168	92	15.46	144	86	12.38
Gastric	Male	16	53	43	2.28	135	85	11.48	157	84	13.19
ulcer	Female	6	38	43	1.63	86	65	5.59	87	61	5.31

[1] 0.10 mg. of histamine acid phosphate given subcutaneously and gastric contents aspirated for 60 minutes beginning when gastric glands first respond.

[2] 16 units of regular insulin given subcutaneously and gastric contents aspirated for 60 minutes beginning when gastric glands first respond.

patients was greater than that in normal individuals and in patients with gastric ulcer, and that, in general, these patients also responded to stimulation by histamine or insulin hypoglycemia by a greater output of gastric juice than was obtained in normal individuals. Some of the data from Ihre's study have been re-calculated and presented in Table II.

In a study recently conducted with my associate, Dr. Harry A. Oberhelman, Jr.,[23] we found that duodenal ulcer patients yield a similarly exaggerated gastric secretory response to a standard dose of histamine. Thus in 18 normal males, an average of 13.2 milliequivalents of hydrochloric acid was secreted in 60 minutes after the subcutaneous injection of one milligram of histamine. In contrast to this, a group of 15 males with peptic ulcer put out 17.3 milliequivalents, and a second group of 18 males with duodenal ulcer put out 27 milliequivalents of hydrochloric acid, or almost twice as much as the normal individual, in response to the same dose of histamine.

Complete division of the vagus nerves to the stomach reduces very markedly the gastric secretory response to a standard dose of histamine as compared with the preoperative level. Thus the first group of ulcer patients secreted 17.3 milliequivalents of hydrochloric acid in response to the subcutaneous injection of one milligram of histamine phosphate before vagotomy, and after vagotomy, the secretion fell to an average of 6.1 milliequivalents,

In the second group of ulcer patients, an average of 27.0 milliequivalents of hydrochloric acid was secreted before vagotomy, and only 5.5 milliequivalents after the operation. A similar effect was found in five total pouch dogs with vagus innervation to the pouch intact. This decreased secretory response of the vagotomized stomach to histamine, which we have customarily thought acts peripherally on the gastric glands, does not necessarily mean that the action is, in part, on the vagus centers. It is conceivable that in some way the sensitivity of the glandular apparatus is reduced by vagotomy so that a humoral stimulus, which acts peripherally, now gives a smaller response than it did before. If it should turn out, as seems likely, that the gastric glands would display the same decrease in sensitivity to the stimulating effect of gastrin after vagotomy that they do to histamine, this procedure should produce a profound decrease not only in the fasting secretion, but in the gastric juice stimulated by the gastric and intestinal phases of secretion as well.

The data in Table I show that the average output of hydrochloric acid in the fasting secretion of ulcer patients is reduced from 60 milliequivalents to 11 milliequivalents per day by complete division of the vagus nerves to the stomach. If we can apply to man the data secured on experimental animals, it seems probable that the output of hydrochloric acid in these cases would be still further reduced from 11 to approximately 3 milliequivalents of hydrochloric acid if the antrum of the stomach were completely excised in addition to the vagotomy. These data bear significantly on the problem of the surgical treatment of duodenal ulcer, since both vagotomy and antrum resection are practical surgical procedures. The evidence is quite clear that complete vagotomy, plus antrum resection, will produce a more profound reduction in the secretion of acid by the fundus of the stomach than can be secured by vagotomy alone. Indeed, in many animals, the combined procedure has been found to abolish almost entirely the secretion of acid gastric juice by the fundus of the stomach.

At present, there appears to be no practical way to eliminate the intestinal phase of secretion in all cases, except, of course, by total gastrectomy. Is complete abolition of all gastric secretion necessary or desirable in the treatment of all cases of peptic ulcer? Does the old dictum, "no acid, no ulcer," also mean "some acid, some ulcer"? This is obviously not the case, since medical management is reputed to deal successfully with the majority of cases of duodenal ulcer, and no one can claim that even the most rigid management achieves complete neutralization of the gastric content at all times during the patient's life. At one extreme, we can cite undoubted, active, duodenal ulcers that respond to a slight modification in the diet and the administration of alkalies. At the other extreme are the ulcers that develop in the ileum, opposite the entrance of a Meckel's diverticulum, containing heterotopic gastric mucosa. In several of these cases, we have seen large, chronic, ileal ulcers, apparently produced by the gastric juice arising from a fragment of gastric mucosa in the diverticulum no larger than one or two

square centimeters. We have also had to treat gastrojejunal ulcers following subtotal gastrectomy where all of the stomach had been removed except for a rim of the fundus no more than four centimeters in length. It is our present view that the marked reduction in acid output in duodenal ulcer patients secured by vagotomy alone suffices for most patients with duodenal ulcers that have proved refractory to medical management. Gastro-enterostomy has been added to the operation primarily to facilitate gastric emptying, and thus simplify postoperative management. This procedure has proved effective except in a small minority of cases, and in these, the vagotomy has usually been found to be incomplete by physiologic tests. While an accompanying or subsequent antrum resection would undoubtedly have produced a further decrease in the secretion of gastric juice, this probably would be inadequate in the presence of an incomplete vagotomy. For these reasons, it seems wiser at present to recommend vagotomy and gastro-enterostomy for cases of duodenal ulcer requiring surgical treatment, and subtotal gastrectomy for the small minority of cases where the more conservative procedure is unsuccessful.

CONCLUSIONS

1. Complete division of the vagus nerve supply to the isolated stomach of dogs reduces the output of hydrochloric acid by an average of 76 per cent. This reduction may also be secured by crushing the vagi above the diaphragm, and it persists for at least two years.

2. Complete removal of the antrum of the stomach in Pavlov pouch dogs decreases the output of hydrochloric acid from the pouch by an average of 86 per cent. This reduction has persisted for two years.

3. Removal of one-half or two-thirds of the antrum does not decrease the secretion of gastric juice in Pavlov pouch dogs, but subsequent removal of the remnant produces a marked decrease in secretion.

4. Exclusion of the antrum of the stomach in Pavlov pouch dogs by a method resembling that of Finsterer and Devine produces no reduction in pouch secretion in 50 per cent of cases and a moderate to marked reduction in the remainder.

5. Exteriorization of the antrum of the stomach so that it does not come in contact with food produces a decrease in secretion comparable to that secured by antrum resection. Subsequent transplantation of the exteriorized antrum into the duodenum brings about a return of secretion from the Pavlov pouch to the original level.

6. Transplantation of the antrum of the stomach into the colon as a diverticulum causes a persistent hypersecretion of gastric juice from the Pavlov pouch.

7. The antrum in totally isolated stomach preparations has no effect on gastric secretion when exposed only to gastric juice, but causes a profound stimulation when transplanted into the duodenum or colon.

8. Transplantation of a portion of the fundus of the stomach into the duodenum has no stimulating effect on the secretion of gastric juice.

9. These findings demonstrate that the antrum of the stomach accounts for the gastric phase of secretion, that its mucous membrane is highly specific in function and differs in this respect from that of the fundus or intestines.

10. The data are in harmony with the view that the antrum is an internal secreting organ which elaborates a powerful gastric stimulant (the gastrin of Edkins) when it comes into contact with food or products of digestion.

11. In normal dogs, the nervous mechanism of secretion probably accounts for 45 per cent of the total amount of gastric juice secreted in 24 hours, the antrum phase 45 per cent, and the intestinal phase 10 per cent or less.

12. In duodenal ulcer patients, the fasting nocturnal secretion of gastric juice is from three to four times greater than normal, and they secrete about twice as much acid in response to insulin hypoglycemia or histamine.

13. Following complete vagotomy, the response to insulin hypoglycemia is abolished, the response to histamine decreased 60 to 80 per cent, and the fasting secretion of hydrochloric acid reduced to one-fifth of the previous level.

14. In duodenal ulcer patients, the nervous phase of secretion probably accounts for 80 per cent of the gastric juice secreted, the antrum phase 15 per cent, and the intestinal phase 5 per cent.

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THE EVALUATION OF END RESULTS IN PHYSIOLOGIC VERSUS PATHOLOGIC OPERATIVE PROCEDURES FOR CHRONIC DUODENAL ULCER DURING THE PAST TWO DECADES*

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A major obstacle in drawing conclusions from operative procedures for chronic duodenal ulcer is the lack of uniformity in the indications for operative intervention in the different procedures. This is understandable when one considers that the end results in the different types of operation are usually based on altered gastric physiology with a lowered free hydrochloric acid or achlorhydria.[1-6] Whether the good results in gastric surgery can be based on altered physiology seems questionable if one has strict indications for referring chronic duodenal ulcers for operation in whom there is, in most instances, an associated pathologic process. Therefore, the results from 1928–1948 inclusive of gastro-enterostomy, sub-total resection, vagotomy, and vagotomy complementary to subtotal resection performed at the Stomach Clinic of the Fourth Medical and Surgical Division of Bellevue Hospital will be reviewed. The policy instituted when the clinic was organized was to exhaust all methods of medical management before any operation would be considered. This policy has been rigidly adhered to, and as a result those cases coming to operation have an associated pathologic process which may alter the end results in certain procedures.

In the late nineteen twenties it was our feeling that gastro-enterostomy was a very satisfactory operation for a chronic duodenal ulcer, even though Lewisohn[7] had reported 34 per cent gastrojejunal ulcers in 1925 and Berg of the same hospital was advocating sub-total resections exclusively for chronic duodenal ulcer. From January, 1928, to December, 1932, inclusive, we had registered 583 cases of ulcers in our clinic; 440 were unoperated cases and 143 had been operated upon previously, but were asked to return for follow-up. Of the unoperated cases, only 33 were referred for operation in five years, or 7.5 per cent. In a later report[8] in which 993 unoperated cases were reviewed, only 14 per cent were referred for operations, which coincides with Allen and Welch, who estimate[9, 10] that 15 to 20 per cent of duodenal ulcers require surgical treatment. Of the 33 patients referred for operation, all had gastro-enterostomies and 29 were performed by the author. It was our feeling then that the regurgitation of bile and pancreatic secretions taking place through the stoma reduced the gastric acidity, thus producing healing of the original ulcer and preventing a gastro-jejunal ulcer. This was in keeping with

* Read before the American Surgical Association, Colorado Springs, Colo., April 20, 1950.

clinical observations of Morton[11] and experimental work of Burget and Steinberg[12] and Elman.[13] The end results of gastro-enterostomy in selected cases was disappointing, and our reports on gastrojejunal ulcer revealed 16.5 per cent[14] with a four and a half year follow-up on 79 patients and 24.5[15] in a 7.1 year follow-up in 106 gastro-enterostomies (Fig. 1).

Since January, 1933, gastro-enterostomy has been completely abandoned as a means of treatment in chronic duodenal ulcer, and sub-total resection was instituted as the sole operative procedure from 1933 to 1945 inclusive. There is a marked divergence of opinion in discussing sub-total gastric resection as

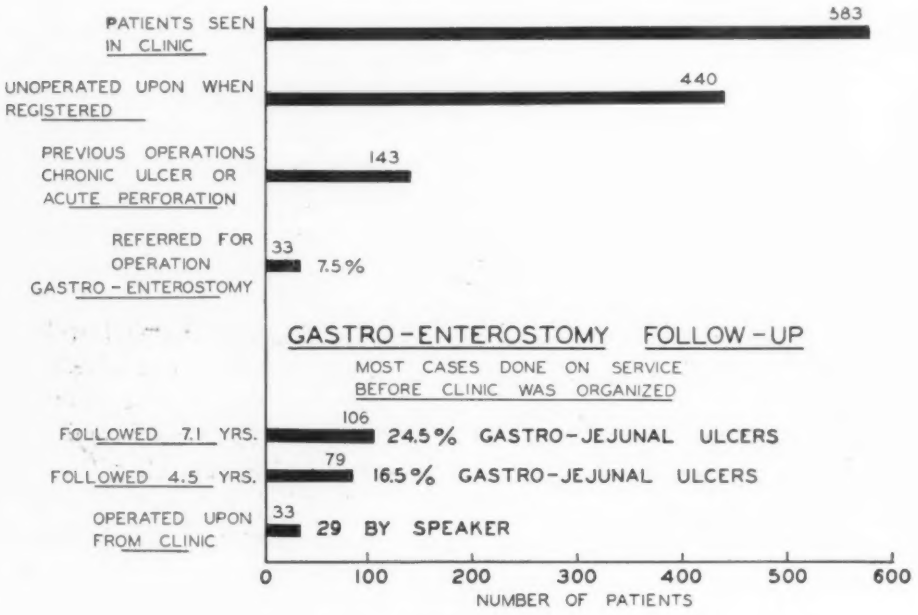

FIG. 1.—1928-1932 inclusive.

to the extent of the stomach which should be removed, the decision as to whether the ulcer may be left in situ or should be removed in toto, and as to the type of gastro-intestinal anastomosis to be established. Although many authors feel the good end results from sub-total resection were based on altered physiology,[16-20] we could not attribute the good results to this alone, when most reports revealed achlorhydria as low as 18 per cent and rarely above 65 per cent.[21-23]

A review of the pathologic findings in the gastro-enterostomies done during the first five years of our clinic was interesting. In the 29 cases done by the author whose symptoms had existed for an average of 7.1 years, it was estimated that 48 per cent were anterior duodenal ulcers, 7 per cent anterior and posterior duodenal ulcers, and 45 per cent purely posterior ulcers. It was immediately seen, when sub-total resections were done, that we had been

wrong in our observations, and in most instances a posterior ulcer and chronic pancreatitis existed and we felt it essential to remove the ulcer in toto to obtain the best end results. A previous report[24] on the first 57 sub-total resections for chronic duodenal ulcer revealed a posterior ulcer in 88 per cent of the cases with an associated chronic pancreas. This should be compared to an estimated 45 per cent of posterior ulcers with gastro-enterostomy in similarly selected cases (Figs. 2 and 3). For the years 1945–1948 inclusive, the incidence of chronic pancreatitis has been 90 per cent in 130 subtotal resections for chronic duodenal ulcer. For that reason we have insisted upon complete removal of the adherent ulcer, as it was felt good results could not be based upon physiologic changes when achlorhydria has been reported in 18 per cent in one series and the more optimistic reports reveal 65 per cent of achlorhydria.

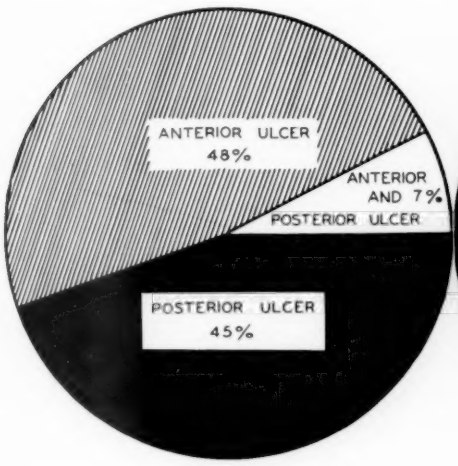

FIG. 2

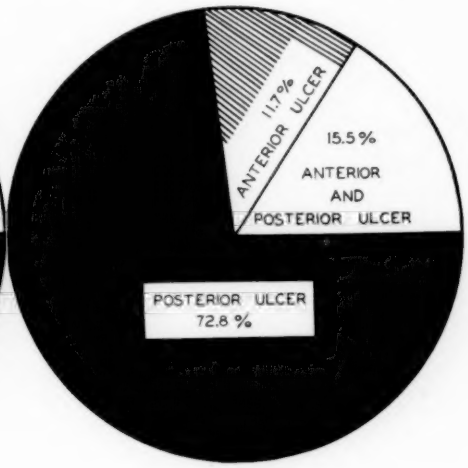

FIG. 3

FIG. 2.—Pathologic process—29 cases. Follow-up: six or 20 per cent, completely asymptomatic in 1.7 year average.

FIG. 3.—Pathologic process in first 57 sub-totals for chronic duodenal ulcer. Chronic pancreatitis in 88 per cent; average age of gastro-enterostomy—37.1 years; average age of sub-totals—37.1 years. Duration of symptoms in gastro-enterostomy—7.1 years; duration of symptoms in sub-totals—7.3 years.

To us it seemed essential to remove the duodenal ulcer from the adherent viscus, in most instances, the pancreas. By removing the ulcer in toto the continuation of the disease process in the pancreas is prevented, and the removal also prevents leaving any of the pyloric mucosa, as may occur if the ulcer is left in situ. If one believes the end results are due exclusively to a reduction of hydrochloric acid or achlorhydria, there is all the more reason for removal of the ulcer in toto, as the likelihood of leaving pyloric mucosa is a real danger when one wishes to obtain a secure closure of the duodenal stump. It is well known from many reports[25-28] that those cases having an exclusion type of operation are more prone to gastrojejunal ulcers. The

chronic duodenal ulcer, which does not have an associated organ involved, rarely needs surgical management. The one exception to this is the duodenal ulcer located on the pyloric muscle which produces excruciating pain and will rarely heal under conservative management; these cases constitute only 5 per cent of ulcers coming to operation in our series.

In an early report of 104 sub-total resections[29] followed on an average of 2.9 years, achlorhydria was present in only 46 per cent of the cases. The end results[30] in 162 sub-total resections for chronic duodenal ulcers, both service and private between 1935 and 1944 inclusive, have been reported. There was an operative mortality of 3.7 per cent and 135, or 86 per cent, of the surviving

TABLE I.—*1933–1944 Inclusive. Sub-total Resections—Removal of Ulcer in Toto.*

Chronic Duodenal Ulcer		
Cases operated upon	162	
Mortality	6	3.7%
Survivals followed, average 3.8 years	135	86.0%
Gastro-jejunal ulcer proved	1	
Gastro-jejunal ulcers suspected	2	
Excellent results	122	90.0%
Achlorhydria		
Cases studied (averaging 2.9 years post-postoperatively)	104	
Achlorhydria on fasting meal	...	46.0%
A chlorhydria after histamine meal	...	15.0%
Gastrojejunal Ulcer or Fistula		
Cases operated upon	27	
Mortality	4	15.0%
Followed (average 4 years)	18	
Re-operated upon	2	11.0%
Moderate hemorrhage	1	
Slight pain-negative x-rays	2	
Excellent results	13	72.0%

patients were followed from one to ten years, average 3.8 years, with one gastrojejunal ulcer and two suspected gastrojejunal ulcers. In this group there were 122, or 90 per cent, with excellent results (Table I).

Since vagotomy has been advocated as the operation of choice in chronic duodenal ulcer by Dragstedt,[31] Moore,[32] and Grimson,[33] this operation has been done as the sole procedure in 35 cases of chronic duodenal ulcer and 19 cases of gastrojejunal ulcer, and as a complementary procedure to sub-total resection in 62 cases. The end results of vagotomy alone, in conjunction with sub-total resection, and sub-total resection alone will be reported for years 1945–1948 inclusive. Since the indications for operation in all three groups were identical, it will give a basis for comparing the end results of a physiologic procedure versus pathologic operation. For this period, I will include both my private cases and the service cases; 60 per cent fell in the former and 40 per cent in the latter. There were 63 sub-total resections for chronic duodenal ulcer

and five sub-total resections for gastro-jejunal ulcers without a complementary vagotomy. Also, 58 sub-total resections in primary duodenal ulcers with a complementary vagotomy and four sub-total resections in gastrojejunal ulcers with a complementary vagotomy were performed. There were 35 transthoracic vagotomies for chronic duodenal ulcers and 17 transthoracic vagotomies for gastrojejunal ulcers and two sub-diaphragmatic vagotomies for gastrojejunal ulcer as the sole operative procedure.

There were five deaths from vagotomy as the sole procedure and four were in primary duodenal ulcers and one in a gastrojejunal ulcer; all occurred in transthoracic procedures. This gives a 9 per cent mortality in 54 cases. None

TABLE II.—*Results of Vagotomy Operations. Side Effects (1) Intermittent Diarrhea, (2) Flatulence and (3) Cardio-spasm.*

Chronic Duodenal Ulcer		
Cases operated upon	35	
Mortality	4	
Recurring diarrhea—total disability	1	
(Patient worked regularly before operation; had 4 hospital admissions of 4–8 weeks; completely studied for other causes, and lost 25 pounds Now 3.5 years postop.)		
Recurring diarrhea—partial disabled	3	
(Average weight loss 12 pounds)		
Failures—recurrence of chronic intractable pain	6	
(Needed subsequent sub-total resections)		
No inconvenience from side effects	21	
(Follow-up 1.8 years average)		
Satisfactory results	11	(35%)
Gastrojejunal Ulcer		
Cases operated upon	19	
Mortality	1	
Subsequent sub-total resections	4	
(Vagal fibers not demonstrated below diaphragm)		
Pain	3	
(Will necessitate further surgery)		
No inconvenience from side effects	3	
Satisfactory results	8	(44.0%)

of the deaths were attributable to technical difficulties of the operations, but to cardio-vascular complications, as two pulmonary emboli were proved by postmortem, two other deaths were suggestive of embolism, and the fifth was due to pneumonia and myocardial insufficiency. When compared to the mortality in sub-total resections, there were two deaths in 130 operations for primary duodenal ulcer and gastrojejunal ulcer with and without complementary vagotomy or a mortality of 1.5 per cent.

The side effects of primary vagotomy in their order of frequency in our series were intermittent diarrhea, flatulence, and cardio-spasm. The diarrhea was of such severity that one patient is still totally disabled at this time, four years later, from recurring severe diarrhea, and five others are, at times, put to great inconvenience and partially disabled. This, plus encountering six failures due to the recurrence of the chronic persistent preoperative pain, which lead to subsequent sub-total resections, led us to abandon the operation as a

sole procedure in late 1947, or less than two years after performing vagotomy as the operation of choice in chronic duodenal ulcer. Whether our poor results are to be attributed to the advanced type of case operated upon or to a possible return of cholinergic action of vagal fibers present in the greater splanchnic and sympathetic chain as the anatomical and histologic studies of Pick[34] suggest in human beings and the animal studies of Duncan[35] also suggests in cats, dogs, and rabbits, is still debatable, but the former seems more plausible.

Vagotomy, as a complementary procedure, has only been done with subtotal resection, as our experience with gastro-enterostomy was so unsatisfactory that we could not persuade ourselves that two physiologic procedures

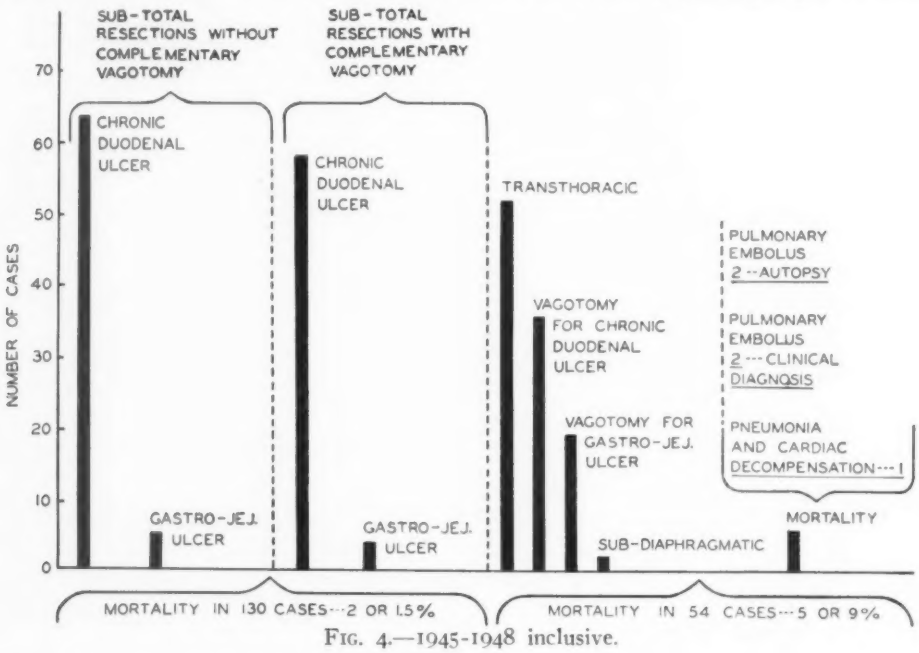

FIG. 4.—1945-1948 inclusive.

would prove satisfactory over a long follow-up. We became convinced that vagotomy as an adjunct to sub-total resection, with removal of the ulcer in toto, would be ideal as a combination of pathologic and physiologic attack on the chronic intractable ulcer. The end results of the different operations done in 1945–1948 inclusive, for both chronic duodenal ulcer or gastrojejunal ulcer, are recorded in Figure 4 and Table II.

The "dumping syndrome" and weight disturbance in the patients with sub-total resection and complementary vagotomy, as compared to sub-total resection, is very striking. Comparing the end results, Table III, of sub-total resection with a complementary vagotomy reveals a higher percentage of under-weight patients and a very high percentage of "dumping syndrome." There were 62 cases with 55, or 89 per cent, followed for an average of 1.7 years. The mechanism of this syndrome has best been explained as a sudden over-distention of the upper jejunum with fluids and particularly with hypertonic glucose solution. Machella[36] explains it as a "jet expulsion" of gastric

contents into the jejunum with an over-distention of the jejunal loop. Likewise, meals with excessive fluids and sugar exaggerate the syndrome, and it is more commonly seen after breakfast in our cases. Machella has produced this syndrome by mechanical distention of the jejunum with a balloon, and also proved that it occurs before hyperglycemia occurs and that the glucose intravenously does not produce this syndrome. Alvarez[37] has observed the syndrome in unoperated cases with sensitive autonomic nervous systems. We have been most disturbed by the high percentage of "dumping syndrome" in

TABLE III.—*1945–1948 Inclusive—"Dumping Syndrome."*

Sub-total with Vagotomy		
Patients	62	
D. S.	15	24.0%
(Five severe enough for partial disability)		
Number patients followed for average of 1.7 years	55	
(Average weight loss 8 pounds)		
Sub-total without Vagotomy		
Patients (with no "Dumping Syndrome")	68	
Followed (average 2 years)	60	88.0%
(Average weight unchanged from preoperatively.)		

the sub-total resections with a vagotomy in comparison to its absence in sub-total resections without vagotomy. It is felt by some that patients develop a sphincteric action[38, 39] after sub-total resection. Others believe the anti-colic Polya anastomosis is a contributing factor in the production of the disturbing sequelae.

TABLE IV.—*1933–1948 Inclusive. All Sub-totals Without Vagotomy.*

Without Vagotomy		
Patients for chronic duodenal ulcer or gastro-jejunal ulcer	257	
Followed (average 4.5 years)	230	88.0%
"Dumping Syndrome" (patient had only slight syndrome)	1	
Gastrojejuna' ulcers		
Proved	2	
Suspected	2	
Total	4	1.7%
(All patients had duodenal ulcers removed in toto)		
Spontaneous choledocho-duodenal fistula	3	
Clinical jaundice from chronic pancreatitis	5	
Evidence of chronic pancreatitis at operation	..	89.0%

Since 1933 we have performed the same type of gastric resection, namely, an anti-colic Polya, short-loop anastomosis averaging 7 to 8 cm., placing the proximal jejunum to the greater curvature and the distal to the lesser curvature and utilizing the entire width of the stomach for an end-to-side anastomosis. In only one instance have we seen a mild "dumping syndrome" in 230 sub-total resections until complementary vagotomy was added to the procedure without other technical changes. Since then we have encountered in 62 sub-total resections with complementary vagotomy 15 cases, or 24 per cent, of "dumping syndrome," with five cases severe enough to produce partial

disability. Vagotomy may prevent the development of sphincteric action which, when present, may prevent the very rapid emptying of the stomach contents into the jejunum and the jejunal dilatation.

The end results from 230 sub-total resections for primary duodenal ulcer as the sole operative procedure (Table IV), with only two definite gastrojejunal ulcers and two suspected cases, were so satisfactory that vagotomy has been discontinued as a complementary procedure because of the severe "dumping syndrome." In six instances it led to partial disability, now one and a half to three years after operation, and nine other patients suffer inconvenience from the syndrome. We feel vagotomy does not have a place in the surgical treatment of chronic duodenal ulcer, but only in superficial ulcers, usually seen in young individuals with massive recurring hemorrhages and an extremely high free hydrochloric acid, 60 to 80 units on a fasting stomach, complete absence of pain, and roentgenologic evidence of a superficial ulcer. These cases are extremely rare, and in the past five years we have encountered only five.

Vagotomy is occasionally used in gastrojejunal ulcer, as a complementary procedure, if the patient has an excessively high acid on a fasting stomach. The pathologic process in chronic gastrojejunal ulcers usually represents the ulcer penetrating into an adjacent viscus, which may be the pancreas, colon, or the mesentery of the colon, and not infrequently it may penetrate into the anterior abdominal wall. In one instance I had occasion to operate upon a 28-year-old man with a perforation of a gastrojejunal ulcer through the left rectus muscle and a free perforation through the skin of 0.5 cm. Vagotomy as the sole procedure in gastrojejunal ulcer was discontinued because of our poor results in 19 cases (Table II).

COMMENT

Comparing the end results in different series of operations for chronic duodenal ulcer is frequently misleading because of the vast differences in the operative indications. In this series the indications for operating upon patients with chronic duodenal ulcer has been the same whether the operation has been gastro-enterostomy, sub-total resection or vagotomy.

One cause of the confusion in the end results from sub-total resections is the fact that many reports are not clear as to what percentage of subtotal resections have left the ulcer in situ. In such cases one has done a physiologic procedure and expects a good end result to result from a lowered free hydrochloric acid or achlorhydria. In this series our end results were most unsatisfactory with gastro-enterostomy in the advanced stages of chronic duodenal ulcer. If the ulcer is left in situ, one should expect similar end results from sub-total resections as seen in gastro-enterostomy.

Some surgeons feel even in massive hemorrhage that good results are obtained from a sub-total resection with the ulcer left in situ. A recent symposium[40] before the New York Surgical Society revealed that patients undergoing such a procedure died from a subsequent hemorrhage, some of them

before leaving the hospital, which would seem conclusive evidence that the ulcer should be removed in these critically ill patients. The massive bleeder which cannot be controlled by transfusions of 2500 to 5000 cc. of blood has a chronic ulcer with penetration into the pancreas in our experience. In 27 patients, personally operated upon since March, 1937, there was one gastric ulcer, two gastrojejunal ulcers, and 24 posterior duodenal ulcers with the superior pancreatico-duodenal artery or one of its large branches eroded through. In five instances the patient was being prepared for surgery in the hospital with a chronic intractable ulcer when the hemorrhage occurred, which was the first in each instance, and not being able to control the hemorrhage by blood replacement, an emergency sub-total gastrectomy was performed. In two other cases the patient was convalescing in the hospital from an acute perforation of an anterior duodenal ulcer when he developed an uncontrollable hemorrhage from a posterior ulcer requiring an emergency sub-total gastrectomy.

In the 27 cases the author has operated upon, there have been six deaths, or a mortality of 22 per cent, and in each patient the ulcer was removed in toto and none of these cases have had subsequent hemorrhage.

In the chronic penetrating ulcer with massive hemorrhage we question the wisdom of ever doing a vagotomy with a gastro-enterostomy. In June, 1947, an uncontrollable hemorrhage from a chronic duodenal ulcer occurred in a 73-year-old male with acute urinary retention requiring a cystotomy, admitted to the former Post-Graduate Hospital, now the University Hospital. While convalescing from the cystotomy with a blood urea of 45 mg. per 100 cc. he had a massive gastro-intestinal hemorrhage. The patient was known to have had a duodenal ulcer for 25 years and after administering 6000 cc. of blood as replacement within 72 hours without controlling the hemorrhage, a laparotomy was performed and a posterior duodenal ulcer was found. A subdiaphragmatic vagotomy and gastro-enterostomy were performed. For 48 hours he did not bleed, but started hemorrhaging again, and in spite of 6000 cc. of blood replacement, succumbed within 72 hours. An autopsy revealed the superior pancreatico-duodenal artery eroded through as the sole cause of death. This case illustrates the necessity of removal of the ulcer in toto in massive hemorrhage from a chronic duodenal ulcer.

The chronic intractable duodenal ulcers which we have had occasion to operate upon have had gastro-enterostomy, sub-total resection with removal of the ulcer in toto, sub-total resection with removal of the ulcer in toto plus a complementary vagotomy, and vagotomy as the sole procedure. The end results from sub-total resection with removal of the ulcer in toto have been so far superior to the other types of operations that we conclude the good results are based upon removal of a pathologic process and not primarily to altered gastric physiology. Since July, 1948, we have reverted to sub-total resection with removal of the ulcer in toto in all chronic intractable ulcers.

CONCLUSIONS

1. Technically it is easier to remove a chronic penetrating duodenal ulcer "in toto" with fewer duodenal leakages than when the ulcer is left "in situ."

2. From reviewing reports on sub-total gastrectomy leaving the ulcer "in situ," it would seem the penetrating ulcer may be partially detached from the pancreas. This, rather than faulty closure of the duodenal stump, explains the cause of leakage.

3. It would simplify the evaluation of end results of sub-total gastrectomy if authors would state whether the ulcer has been left "in situ" or removed "in toto," and likewise what percentage of the stomach was removed.

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THE EFFECT OF DEFINITIVE SURGERY ON DUODENAL ULCER DISEASE

A COMPARATIVE STUDY OF SURGICAL AND NON-SURGICAL MANAGEMENT IN 997 CASES*

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WITH FEW EXCEPTIONS, the natural history of a malignant process terminates in the death of the host; the success of treatment would not appear difficult to assess. In the older age group any attempt to evaluate surgery surprisingly belies this simplicity, since death from other causes may remove the statistical unit from the scene before it can be classified. Despite this difficulty, the statistical problem in malignancy is a relatively simple one because of the high mortality and readily demonstrable evidence of recurrent disease. Much surgical thought has been influenced by our habitual concept of success in malignancy: survival is the objective. We search for operative survivals or for "cure rates," often considering that after five years survival and cure are synonymous.

In dealing with a benign process such as duodenal ulcer, the vast majority of patients may be expected to succumb to other causes; the natural history of the disease terminates as a cause of death in only a small (but significant) number of patients, and some sort of symptomatic or economic criterion must be used for success with the remainder. Although it is common knowledge that duodenal ulcer is a life-long recurrent disease, and although this statement is repeatedly made in the literature, there are surprisingly few facts available which prove that any form of treatment has altered this life-long history.

In medicine generally and in the medical treatment of ulcer in particular, a life-long rapport between patient and physician is necessary to realize the best results. A physician counts his work well done if, with little risk, the patient has been saved from the surgeon's scalpel or from the autopsy table; but he should remain a patient. The concept of discharge is indistinctly seen on the distant horizon.

The surgeon's objective, by assuming a much greater immediate risk, is to free the patient from the physician and from the surgeon alike, and cast

* Read before the American Surgical Association, Colorado Springs, Colo., April 20, 1950. This investigation was supported by a research grant from the National Institutes of Health, Public Health Service. The authors acknowledge their debt to Dr. J. H. Means and Dr. C. M. Jones for making available for this study the records of 952 patients from the Medical Service and Medical Gastro-Intestinal Clinic of the Massachusetts General Hospital.

him loose again into the main stream of society well, as a citizen rather than as a patient. This difference in viewpoint has been fruitful of much controversy and it must be bridged in order to bring the total problem into focus and discover whether either the physician or the surgeon accomplishes his objective.

Despite the fact that the doctor treating duodenal ulcer is trying to intervene in a disease which has a long and complicated life history, attention in the literature has remained focussed on technics in all fields of therapy. Whether the physician uses alkalies, midnight aspirations or enterogastrone is a source for discussion exactly akin to the question of whether the surgeon shall do his anastomosis anterior or posterior to the colon or whether he shall do a vagotomy with his gastro-enterostomy. Such questions of technic have important short-term significance, particularly in surgery, where they may influence the mortality. As the years go by their importance shrinks and a more fundamental problem begins to emerge which can be stated as follows: "Has the doctor's treatment altered the life history of the patient's disease or has it been merely an episode in a long series of remissions and exacerbations?" Such was the genesis of this study.

It is our purpose to record a statistically significant group of cases taken from this hospital, followed up by the same method, and success judged by the same criteria in both medically and surgically treated patients. Since conditions in hospitals differ, each clinic must turn the mirror upon itself to establish norms, and lay down the criteria by which improvements in method may be judged.

In this study we have sought several objectives:

1. To examine a sizable group of ulcer patients regardless of the mode of treatment or the nature of the complications, so as to discern the outcome of the disease process.

2. To apply to all cases the same criteria of success and failure.

3. To discern within a single frame of reference whether the doctor improves the outlook of the patient or indeed alters in any way the course of the disease.

MATERIALS AND METHODS

A. Clinical Selection. To accomplish the purpose of this study, an unselected group of duodenal ulcer patients was needed, recent enough in date to include present methods of treatment, old enough to be viewed in perspective and to give some duration for follow-up. All patients with a proved duodenal ulcer or with ulcer deformity of the duodenum demonstrated by roentgenogram (with or without a crater) seen in the wards or Out-patient Department of the Massachusetts General Hospital in the years 1942 to 1946 inclusive formed the material of this research. It then remained to discover the source of these patients and evaluate their course subsequent to the 1942–46 episode (or episodes) at the Massachusetts General Hospital.

Gastric ulcers were excluded from the study. Patients suspected of duodenal ulcer by symptom, unproved by roentgen ray, were excluded; patients

entering for other complaints and found to have duodenal ulcer incidentally were included in the study, although they are few in number. Thirty-eight patients with gastro-jejunal ulcer are included without separate classification, providing the jejunal ulcer developed after surgery for duodenal ulcer. If jejunal ulcer arose under other circumstances it was excluded from the study. Private patients were excluded.

B. Origin and Subsequent Course. This group of patients numbered 1246. Their origins could be described in general as a graded series of case histories ranging from those few patients who had no gastro-intestinal symptoms and only a roentgenographic finding of ulcer, through the group entering the hospital at the time of their first symptoms (not infrequently hemorrhage or perforation), and progressing on to that large group of patients who had been suffering ulcer symptoms for years, often with complications, and in a few cases with previous attempts at definitive surgery.

While under care at the Massachusetts General Hospital during the 1942–46 period, their courses were equally divergent. At the one extreme were those patients treated not at all for ulcer because of other more important disease, although hardly one escaped without an admonition to follow an "ulcer diet." Many patients were treated as out-patients; a large number entered the hospital for one admission and were then followed in the out-patient department. At the other extreme of therapeutic endeavor lay those many patients having multiple house admissions, intensive treatment, consultation with gastro-intestinal specialists, psychiatric interviews, and finally definitive surgery. A small number died of their ulcers while in the hospital.

Subsequent to their therapeutic adventures in the 1942 to 1946 period under study, a variety of fates awaited this group of patients. It is the detailed consideration of this subsequent fate which permits the classification as to success or failure as described below. Some patients were "lost," meaning that they either died of other causes before progress could be evaluated or that insufficient data were accumulated. A number died of ulcer at other hospitals and many were lost track of by hospital record but were readily uncovered by follow-up letters. Not a few of these had undergone definitive surgery elsewhere. Then, finally, there was that large group of faithful patients whose courses right up to the time of evaluation could be ascertained from a complete hospital follow-up record, together with an interview at an outpatient visit.

C. Methods of Follow-up Study. Had we confined our evaluation of events since the 1942–46 period entirely to the hospital record, much of interest would have been lost. It soon became apparent that in dealing with duodenal ulcer "no news is bad news."* Many whose hospital records ceased after an

* There is a point here of more general interest: physician and surgeon alike base an "impression" of result in personal cases on those followed in office or clinic. Such is a self-selected group and will invariably leave the doctor with a specious impression of success. The untraced 13.4 per cent in this series should accordingly be viewed with suspicion.

uneventful house admission and a few follow-up clinic visits were found to have had repeated exacerbations later, often with admissions to other hospitals for complications or surgery. A few had definitive surgery elsewhere and several of the "late ulcer deaths" in the non-operative group were uncovered only by personal follow-up and examination of official records at the State House.

In order to discover these facts, all patients were sent a letter with a questionnaire giving them (or their survivors) an opportunity to express an opinion as to progress and present status. To this information was added a personal interview whenever possible and the results of whatever other data (roentgenograms, clinic visits) could be brought to bear on the problem.

D. Categories Studied. All the cases were divided into four categories based on the predominent therapeusis carried out at the Massachusetts General Hospital in 1942–1946.

Category 1—Non-surgical Management. None of these patients received definitive surgery at the Massachusetts General Hospital in 1942–1946.

Category 2—Acute Perforation. Patients treated at the Massachusetts General Hospital for acute perforation in 1942–1946 were placed in this category. None in this category received definitive surgery at the Massachusetts General Hospital in 1942–1946, and for this reason the group is in many respects a subdivision of category 1.

Category 3—Subtotal Gastrectomy. Patients having subtotal gastrectomy at the Massachusetts General Hospital in 1942–1946 fell into this category.

Category 4—Vagus Resection. Vagotomy performed at the Massachusetts General Hospital in 1942–1946 determined placement in this group.

E. Terminology. The term "non-surgical management" is deliberately ambiguous. Of this large group only a few could be considered as having "ideal medical treatment" and hence avoidance of the latter term; the task of giving perfect medical management to this large group would have been overwhelming to the facilities available. So few received other than casual treatment or sporadic follow-up (even after an intensive hospital experience) that category 1 may approximate in its main features the natural history of duodenal ulcer disease.

The term "definitive surgery" denotes an operation undertaken to alter the development of the disease process. Subtotal gastrectomy and vagus resection were the only procedures used at the Massachusetts General Hospital in 1942–1946. Operation to close perforation does not fall into this category; operation to stop hemorrhage is classed as definitive, providing a procedure was carried out which at the same time satisfied the anatomic requirements of an elective subtotal gastrectomy. Just as the medical care of these patients should not be thought of as "ideal," so also the surgical operations should be regarded in the light of the fact that they were largely carried out by the resident staff. The hospital policy of presenting to young doctors

experience under supervision prevents the continuity of medical treatment or standardization of surgery found in private clinic or practice. It is the opinion of the authors that this factor operates to the detriment of long-term medical treatment more than it does in surgical care.

F. Classification of Results. Based on all the information available, the trend of the patient's disease since his Massachusetts General Hospital episode of 1942–1946 was classified. This required a subjective judgment on the part of the observer. The patient's own account of his degree of deficit or rehabilitation usually did not conflict with a physician's evaluation. When it did, a choice had to be made. Each result was independently rated by at least two observers, who based their estimates on the most recent 80 per cent of the follow-up period. Except for ulcer deaths, no result shorter than two years was rated; follow-up periods range from two to eight years in all categories. The following classification of results was used, employing four classes:

Class I. Excellent. The patient appears to be completely free of his disease, with no restrictions on his manner of living any more than if he had never had a duodenal ulcer at all; asymptomatic *without* ulcer regimen. Not a patient any more.

Class II. Good. The patient is able to qualify as having an excellent result only by observing some sort of ulcer regimen. This may vary from a rigid diet and medication to modification of smoking habits or the avoidance of certain foods. In other words, asymptomatic *with* ulcer regimen; still a patient, but well.

Class III. Fair. Though improved, the patient cannot or will not qualify as having an excellent or good result; improved but still symptomatic. An ailing patient. Two subgroups are used, which follow.

Class III (a). In this group are patients with mildly incapacitating symptoms, such as those causing the loss of an occasional day from work but not more than seven days in the most recent year. Symptoms due to unavoidable emotional stress or fatigue, mild "dumping" symptoms, and poor appetite also qualify for this group. (*b*) Patients who are somewhat underweight but not enough to interfere with their normal activities or to present a medical problem are considered as having a III b result. This group is small because even in the presence of a slight weight deficit, other factors are usually more important in determining the result.

Class IV. Poor. The patient's disease is unimproved, worse or fatal. This is a dissatisfied patient. Reasons for classification as Poor are seven, listed as seven subgroups: (a) Hospital death following a definitive ulcer operation or suture of a perforated ulcer at the Massachusetts General Hospital. (b) Death from ulcer or its complications other than the above. (c) Major ulcer complications not yet fatal, such as stomal ulcer, hemorrhage, obstruction, perforation or intractable pain, developing or continuing in spite of attempted treatment; subsequent definitive ulcer surgery. (d) Severely underweight,

in itself constituting a disability. (e) Ulcer symptoms producing economic incapacity amounting to the loss of more than 14 days' work in the most recent year. (f) Persistent distress or disability resulting from ulcer therapy, such as disabling unrepaired incisional hernia, painful scar, malfunctioning anastomosis, severe "dumping" syndrome amounting to a crippling disorder, neuritis, diarrhea, anemia, etc. (g) Definite dissatisfaction with the result on the part of the patient or the evaluators for some reason or combination of reasons not specified above.

It should be emphasized that the mere recurrence of a duodenal crater by roentgen ray is not taken as evidence of failure in medical management; such a criterion would confer an overwhelming incidence of failure in the non-surgical cases. An ulcer crater should rightly be accompanied by crippling or endangering manifestations to be indicative of medical failure. Recurrent ulcer or stomal ulcer is universally regarded as evidence of surgical failure and is so classed here regardless of other manifestations.

A word is necessary concerning our use of "subsequent definitive surgery" as a criterion of failure (Class IV c): if a patient had definitive surgery at the Massachusetts General Hospital in 1942–1946. This is not rated as a failure of *previous* medical or surgical treatment. If, on the other hand, he had either medical or surgical care at the Massachusetts General Hospital, 1942–1946, and *subsequently* required resection or re-resection, this is rated as a "Poor" (Class IV c) result of his 1942–1946 treatment. Similarly, perforations cared for at the Massachusetts General Hospital in 1942–1946 are not rated as failures of previous non-operative management. On the other hand a patient known to have duodenal ulcer in 1942–1946 and treated medically or surgically at the Massachusetts General Hospital who subsequently perforates, is rated as "Poor" (Class IV c). Finally, postoperative mortality is always listed as a surgical failure (IV a) regardless of how many years of non-surgical management contributed to the age and debility of the patient or the anatomic complexity of the procedure.

Classes I and II (Excellent and Good) are taken together as "Satisfactory Result"; classes III and IV (Fair and Poor) as "Unsatisfactory Result." Patients who died from other causes less than two years after their Massachusetts General Hospital 1942–1946 episode were excluded from classification as yielding insufficient data for classification.

A simple system of coding is possible within this framework, *e.g.*, a "3-IV c" result means that a patient having a subtotal gastrectomy at the Massachusetts General Hospital in 1942–1946 is rated as a poor result because of subsequent major ulcer complications or surgery.

G. Statistical Methods. The work of Hollander and Mage[1] and later of Cooper,[2] Heuer[3] and others[4-10] point up some of the pitfalls of statistical method in such a study. Since we are grading a set of results in four categories of patients treated concomitantly, differences in follow-up period

between the groups do not upset the comparative values. The follow-up period is two to seven years in all groups except the small and statistically insignificant vagotomy series, where it is two to five years. The doctrine of "once a failure always a failure" applies for Class IV a, IV b and IV c results (death, major ulcer complications, or subsequent definitive surgery); for other types of results the "most recent 80 per cent of the follow-up period (at least two years)" is used. Since this method is used on all cases it does not introduce any disparity between the series.

Our follow-up method, as mentioned previously, uncovered many failures not documented on the hospital record, thus disproving (if any further disproof were needed) the contention that "lost" cases may be assumed to have done as well as the traced cases.

The only statistical problem remaining is the comparison of percentages between two series of patients of differing numerical size. To establish significance between groups, the probability ratio was determined as follows:

s_1 = Standard deviation of a percentage
P_1 = Percentage in N, number of cases
Then:

$$s_1 = \sqrt{\frac{P_1\ (100 - P_1)}{N_1 - 1}}$$

For standard deviations (s_1 and s_2) of two series, the probability ratio (P.R.):

$$\text{P.R.} = \frac{P_1 - P_2}{\sqrt{{s_1}^2 + {s_2}^2}}$$

A P.R. of 2.6 or higher indicates a 99 per cent (or greater) probability that the difference in the percentages is a phenomenon due to factors other than chance.

The results so compared cannot be regarded in any sense as final for the series. In this group of patients suffering from a benign disease the final result cannot be tabulated until all 1246 patients have died.

RESULTS

A. Number of Patients Studied. The 1246 patients whose records were abstracted grouped themselves in the four categories of treatment as follows (Table I):

Category 1. Patients receiving no attempt at definitive surgical treatment at the Massachusetts General Hospital during 1942–1946—952 cases.

Category 2. Patients admitted to the Massachusetts General Hospital, 1942–1946, because of acute perforation of a duodenal ulcer—85 cases.

Category 3. Patients receiving subtotal gastrectomy at the Massachusetts General Hospital, 1942–1946—175 cases.

Category 4. Patients receiving vagus resection at the Massachusetts General Hospital, 1942–1946—34 cases. All of these were transthoracic operations without gastro-enterostomy.

B. Success of Follow-up. Although 1080 patients (86.6 per cent) of the 1246 cases were successfully traced, in only 997 cases (80 per cent) were sufficient data obtained to justify classification of the results in terms of ulcer treatment. Eighty-three patients died of other causes and 44 of these succumbed to other pathologic processes before a result in terms of ulcer care could be classified on the basis of two-year follow-up. Thirty-nine patients, although followed satisfactorily, could not be classified because of conflicting or incomplete information. Patients dying of duodenal ulcer were rated as deaths due to ulcer (Classes IV a or IV b) regardless of when they occurred.

C. Success of Treatment. In Tables II-A and II-B is shown a brief summary of the results obtained in the 997 classified patients. Of the entire group,

TABLE I.—*Duodenal Ulcer, 1942–1946. Cases Studied.*

Category	Total	Followed	Classified	Deaths	Ulcer Deaths
1 Non-surgical	952	807	738	82	15
2 Perforating	85	77	70	15	8
3 Subtotal gastrectomy	175	162	155	12	5
4 Vagus resection	34	34	34	2	0
Totals	1246	1080	997	111	28

Per cent followed, 86.6; per cent classified, 80.

Death rate in followed patients, 10.3 per cent; ulcer death rate in classified patients, 2.8 per cent; per cent of total deaths due to ulcer, 25.2.

Note: The 83 patients followed but not classified include 44 patients who died from other causes before an ulcer result could be classified on the basis of two years' follow-up and 39 followed patients in whom no valid judgment could be made as to result.

about one-half (51.4 per cent) had pursued a course since 1942–1946 which could be termed satisfactory, by which was meant that their results fell either into Class I or Class II. The remaining 48.6 per cent fell into Classes III or IV and must be termed unsatisfactory. In those patients in whom no definitive surgery was carried out (Category 1), 45.6 per cent achieved a satisfactory result and 15.1 per cent an excellent result. In those patients in whom subtotal gastrectomy was carried out, 76.1 per cent achieved a satisfactory result and 53.5 per cent an excellent result. This difference is significant statistically, with a probability ratio of 6.8.

D. General Mortality. Of the 1080 patients traced, 111 are known to be dead. Twenty-eight of these 111 deaths (25.2 per cent of the deaths) are known to have been due to duodenal ulcer or its complications and the remainder due to other causes. These 28 deaths represent an overall ulcer mortality of 2.8 per cent for the 997 cases in which the details are accurately known.

Among those patients who did not receive definitive surgical treatment (Category 1) there was an ulcer mortality of 2.03 per cent. None of the patients who died of perforation had received definitive surgical treatment and when

these two categories (1 and 2) are added, the total mortality in patients managed without definitive surgical treatment at the Massachusetts General Hospital, 1942–1946, is found to be 2.85 per cent. As will be described later, this figure should be revised downwards in the light of several of the case histories which included no opportunity for either medical care or definitive surgery.

Among the 175 subtotal gastrectomy patients, a hospital mortality of 2.86 per cent was encountered; none of the traced cases died subsequently of ulcer.

TABLE II-A.—*Duodenal Ulcer, 1942–1946, Total Results by Four Classifications.*

	Category	Number Classified	Class I Excellent		Class II Good		Class III Fair		Class IV Poor	
1	Non-surgical	738	111	15.1%	225	30.5%	161	21.8%	241	32.6%
2	Perforating	70	13	18.6%	21	30.0%	17	24.3%	19	27.1%
3	Subtotal gastrectomy	155	83	53.5%	35	22.6%	18	11.6%	19	12.3%
4	Vagus resection	34	11	32.2%	13	38.3%	4	11.8%	6	17.7%
	Totals	997	218	21.9%	294	29.5%	200	20.0%	285	28.6%

There were no deaths in the small series of vagotomies for duodenal ulcer, although two of the patients subsequently succumbed to other diseases.

The mortality of definitive surgery at the Massachusetts General Hospital, 1942–1946, is therefore 2.39 per cent of operations, 2.65 per cent of classified cases, or 2.86 per cent of subtotal gastrectomies.

Regardless of which basis is chosen for computing the ulcer deaths in the surgical cases as versus those patients who did not receive definitive surgery,

TABLE II-B.—*Duodenal Ulcer, 1942–1946, Total Results by Two Classifications.*

	Category	Number Classified	Satisfactory Classes I and II		Unsatisfactory Classes III and IV	
1	Non-surgical	738	336	45.6%	402	54.4%
2	Perforating	70	34	48.6%	36	51.4%
3	Subtotal gastrectomy	155	118	76.1%	37	23.9%
4	Vagus resection	34	24	70.5%	10	29.5%
	Totals	997	512	51.4%	485	48.6%

there is no statistically significant difference in mortality between the two groups. A comparison of the lowest non-surgical mortality (2.03 per cent in 738 cases) with the highest surgical mortality (2.86 per cent in 175 cases) yields a probability ratio of 0.6, which is far below the significance level.

PATTERNS OF FATALITY

Having examined the overall statistical results, it is worth-while turning our attention to the anatomy of failure. This can only be done by shifting from group statistics to a discussion of those individual cases who succumbed to this disease. We can then ascertain whether or not any consistent pattern emerges; these brief histories of fatal cases are of importance in discovering those sorts of phenomena which lead to death. The fatal cases will be discussed

in each category of treatment. Following each history a note as to interpretation is given; these notes are further clarified in the next section.

Category 1.—Patients who received no definitive surgery at the Massachusetts General Hospital, 1942–1946. There were 15 such deaths as follows:

Case 1.—D. C., 201,829, was a male, age 58, with an 18-year ulcer history, including perforation in 1926 and hemorrhage in 1931 and 1942. He died 1943 (Massachusetts General Hospital) of pyloric obstruction and pyelonephritis. Postmortem was obtained. (Preventable, salvageable).

Case 2.—J. M., 315,297, was a male, age 69, with a 35-year ulcer history, including pyloric obstruction in 1939, for which a posterior gastro-enterostomy was carried out at another hospital; jejunal ulcer was observed in 1942 and hemorrhage occurred. Subtotal gastrectomy was evidently not considered at this time, nor were the surgeons consulted. The patient died in 1944 (at another hospital) of perforated ulcer, intestinal obstruction, and pneumonia. (Preventable, salvageable).

Case 3.—E. M., 368,152, was a male, age 39, with a 7-year ulcer history, including two perforations in 1938 and 1941 respectively. He died in 1945 (at another hospital two years after Massachusetts General Hospital admission for ulcer), following operation for perforation and acute massive hemorrhage. No postmortem was obtained. While in this hospital under study the patient was admitted to the emergency ward, and despite two previous perforations, no concerted attempt was made to guide him into adequate treatment. (Preventable, salvageable).

Case 4.—E. C., 416,300, was a male, age 35, with an ulcer history of 4 years or more, including one perforation. He had suffered from pyloric and intestinal obstruction since his perforation. He was a chronic intestinal invalid, having had 8 laparotomies for ill-defined reasons. He died in 1947 (at another hospital) after operation to relieve obstruction. No postmortem was obtained. While in this hospital for study, the patient was extremely unco-operative and was discharged against advice. (Non-preventable, salvageable).

Case 5.—D. C., 384,256 was a female, age 76, with a history of duodenal ulcer with appropriate roentgen ray findings of long standing, concomitant chronic alcoholism, cirrhosis of the liver, arteriosclerotic heart disease and psychotic states. She died in 1949 (at another hospital) of peritonitis secondary to a perforated viscus. Clinical diagnosis was perforated ulcer. No postmortem was obtained. (Non-preventable, non-salvageable).

Case 6.—A. H., 391,873, was a male, age 86, with no history of duodenal ulcer. He died in 1943 (Massachusetts General Hospital) of hemorrhage, 28 days after admission to the hospital because of acute cardiac decompensation. Postmortem examination revealed a bleeding duodenal ulcer. Ten days previously a gastro-intestinal roentgenogram had been negative. (Non-preventable, non-salvageable).

Case 7.—H. M., 397,548, was a male, age 52, with a 5-year ulcer history. He died in 1943 (Massachusetts General Hospital), 5 days after a duodenectomy and pancreatectomy undertaken with the erroneous diagnosis of cancer of the second portion of the duodenum. Diagnosis on the surgical specimen: duodenal ulcer of the second portion of the duodenum with large inflammatory mass and penetration into the head of the pancreas. No postmortem was obtained. (Preventable, salvageable; a diagnostic error).

Case 8.—J. R., 394,893, was a male, age 42, with a 10-year ulcer history. He was hospitalized for bleeding at the Massachusetts General Hospital, at which time no surgical consultation was requested. He was discharged to the Out-patient Department on dietary

treatment. Three months later he suffered a perforation and died (at another hospital) of peritonitis. Postmortem examination was obtained. (Preventable, salvageable).

Case 9.—J. B., 457,012, was a male, age 74, with an ulcer history of unknown duration. He died in 1944 (Massachusetts General Hospital), one hour after admission. He was in shock due to acute massive hemorrhage on admission. Postmortem examination revealed a bleeding duodenal ulcer. (Non-preventable, non-salvageable).

Case 10.—D. S., 319,914, was a male, age 60, with an ulcer history of at least 3 years' duration. He underwent combined abdomino-perineal resection for carcinoma of the rectum 6 years previously, was treated at the Massachusetts General Hospital about one month previous to death, and had had previous acute massive hemorrhage. He died in 1947 (at home) of acute massive hemorrhage leading to hemiplegia and death. No postmortem examination was obtained. (Non-preventable, non-salvageable).

Case 11.—J. C., 425,641, was a male, age 77, with an ulcer history of 3 years' duration, including massive hemorrhage under very careful and persistent medical supervision. Throughout his illness, the patient was also suffering from arteriosclerotic heart disease. He died in 1949 (Massachusetts General Hospital) of acute massive hemorrhage. Generalized arteriosclerosis and senile dementia were present. No postmortem was obtained. (Non-preventable, non-salvageable).

Case 12.—G. G., 187,384, was a male, age 74, with no ulcer history, although he had previous appendicitis and cholecystitis. He died in 1945 (Massachusetts General Hospital), 3 days after admission for acute massive hemorrhage. The patient fainted when he began to bleed and sustained a fracture of the left side of his head and face as a complicating factor. Postmortem revealed a bleeding duodenal ulcer. (Non-preventable, salvageable).

Case 13.—H. M., 433,380, was a male, age 48, with an ulcer history of 7 years, with perforation 7 years previously. He died in 1945 (at another hospital) of ulcer, one year after the last Massachusetts General Hospital admission, at which time roentgen ray showed an active ulcer crater. No postmortem was obtained. (Preventable, salvageable).

Case 14.—D. Q., 174,017, was a male with a 13-year ulcer history, including hemorrhage 10 years previously. He died in 1945 (Massachusetts General Hospital) one day (age 72) after admission for acute massive hemorrhage. Postmortem revealed a bleeding ulcer, cardiac infarction, bronchopneumonia and pulmonary edema. (Preventable, non-salvageable).

Case 15.—P. C., 528,442, was a male, age 44, with a 6-year ulcer history, who died in 1946 (at home), 23 days after Massachusetts General Hospital admission. The Massachusetts General Hospital admission was for undiagnosed abdominal pain. The patient died of a perforated duodenal ulcer with peritonitis, proved by postmortem examination carried out in the patient's home. (Preventable, salvageable).

Category 2.—Patients who had received no definitive surgery at the Massachusetts General Hospital, 1942–1946, and who died at the Massachusetts General Hospital following acute perforation. There were eight such deaths as follows:

Case 16.—E. H., 401,617, was a male, age 72, who was admitted to the ward for arteriosclerotic heart disease, not in congestive failure. While on the ward the patient perforated and died in 2 days of generalized peritonitis. There was no operation. Postmortem revealed a perforated ulcer which had not been suspected prior to death. (Non-preventable, non-salvageable).

Case 17.—W. W., 276,099, was a male, age 82, with a one-year ulcer history, including hemorrhage on one occasion. He died (Massachusetts General Hospital), 12 hours after admission, of perforated duodenal ulcer with peritonitis. No operation was performed. Postmortem revealed perforated ulcer with peritonitis, coronary thrombosis, and an old inactive rheumatic endocarditis. The patient also had diabetes mellitus. (Preventable, non-salvageable).

Case 18.—E. C., 498,534, was a male, age 76, with a 20-year ulcer history, who died in 1945 (Massachusetts General Hospital), less than one day after admission, of perforated duodenal ulcer. No operation was performed. Postmortem revealed a perforated ulcer with peritonitis. The patient was admitted with perforation of 3 days' duration and in moribund condition. (Preventable and salvageable on the basis of history; a lost cause tactically in the final episode).

Case 19.—F. W., 43,804, was a male, age 47, with an 18-year ulcer history including admission 13 years previously for duodenal ulcer. He died in 1945 (Massachusetts General Hospital) 72 hours after suture of a perforated ulcer. The clinical episode suggested re-perforation, and for this reason re-exploration was carried out just before death. No postmortem was obtained. (Preventable, salvageable).

Case 20.—W. L., 221,452, was a male, age 54, with a 13-year ulcer history, including admission for ulcer one year previously. He died in 1947 (Massachusetts General Hospital) on the twelfth postoperative day, after suture of an acute perforation of duodenal ulcer. The patient also had pyloric obstruction, portal cirrhosis and ascites. No postmortem was obtained. (Preventable, non-salvageable).

Case 21.—E. T., 553,430, was a male, age 42, with no previous history of duodenal ulcer. He died on the sixth day after suture of perforation, of extending peritonitis and bronchopneumonia. Postmortem was obtained. (Non-preventable, salvageable).

Case 22.—M. C., 452,564, was a male, age 30, with a 15-year ulcer history complicating rheumatic heart disease. He died in 1944 (Massachusetts General Hospital), the sixth postoperative day after suture of perforation. Postmortem revealed peritonitis with bronchopneumonia and inactive rheumatic heart disease. (Preventable, salvageable).

Case 23.—H. L., 337,257, was a male, age 54, with an unknown duration of history. He died in 1942 (Massachusetts General Hospital), 7 days after operation for perforated viscus. The patient had been admitted the previous month because of active duodenal ulcer with bleeding. He was discharged home after 12 days' treatment and re-admitted within 4 days because of acute massive hemorrhage. Thirteen days after admission an acute perforation occurred which led to his death. Postmortem disclosed an active duodenal ulcer with perforation, and fecal impaction with necrosis of the bowel wall and simultaneous perforation of the sigmoid. The recently perforated duodenal ulcer had sealed over. (Preventable, salvageable).

Category 3.—Death following subtotal gastrectomy carried out at the Massachusetts General Hospital, 1942–1946. There were five such deaths as follows:

Case 24.—G. A., 384,686, was a male, age 49, with a 23-year ulcer history with very consistent medical treatment. Posterior gastro-enterostomy was carried out in 1929 at another hospital followed by the development of a jejunal ulcer. He died (Massachusetts General Hospital) 15 days after subtotal gastrectomy, of pulmonary embolus. No postmortem was obtained. (Preventable, salvageable).

Case 25.—J. D., 395,116, was a male, age 54, with a 13-year ulcer history with a gastro-enterostomy carried out in 1940 at another hospital. The patient also suffered

from chronic alcoholism and psychosis. Five months prior to that a volvulus of the small bowel occurred and small bowel was resected. One month later the patient was admitted for elective surgery. The old gastro-enterostomy, which turned out to have been a gastro-ileostomy, was taken down. Three months after this episode, the patient entered with acute massive hemorrhage from reactivated duodenal ulcer. A subtotal gastrectomy was carried out and the patient died of acute massive hemorrhage on the fifth postoperative day. The postmortem revealed bleeding duodenal ulcer, the ulcer crater having been left in at the time of the subtotal gastrectomy. (Preventable, salvageable).

Case 26.—G. F., 492,366, was a male, age 50, with a 3-year ulcer history. He entered with pyloric obstruction, and died in 1945 (Massachusetts General Hospital) ten days after subtotal gastrectomy. He died with an episode of vomiting and convulsions. The postmortem did not include the brain and revealed pulmonary edema. A cerebrovascular accident could have been a contributory cause of death; the patient's postoperative course was stormy and febrile with questionable patency of the operative stoma throughout. (Preventable, salvageable).

Case 27.—J. W., 555,507, was a male, age 60, with a 20-year ulcer history with massive hemorrhage, 12, 5 and 3 years prior to admission. He was admitted with pyloric obstruction. He died in 1946 (Massachusetts General Hospital) 27 days after subtotal gastrectomy, of peritonitis secondary to inadvertent operative interruption of the bile ducts in a difficult duodenal dissection. Postmortem was obtained. (Preventable, salvageable, and tactically would have been a simpler problem if surgery had been undertaken earlier in the history of the disease).

Case 28.—D. M., 14,717, was a male, age 76, with a 45-year ulcer history with 4 previous hemorrhages. He died in 1942 (Massachusetts General Hospital) following subtotal gastrectomy for duodenal obstruction, of bronchopneumonia and peritonitis. No postmortem was obtained. (Preventable, salvageable and tactically would have been a simpler problem if surgery had been undertaken earlier in the history of the disease).

Discussion of Deaths. From these 28 deaths two distinct patterns emerge —one takes the form of a young or middle-aged man in the prime of life, who succumbs to a complication of which his physicians have been forewarned by a long and virulent ulcer history. These deaths are preventable deaths in salvageable patients. The other pattern is that of an elderly male with a short or non-existent ulcer history often with complicating pathologic conditions in vital organs, a patient who, on the basis of other serious disease, may be regarded as non-salvageable.

Of the 15 deaths in patients of category 1 (no definitive surgery at the Massachusetts General Hospital, 1942–1946) seven (cases 1, 2, 3, 7, 8, 13 and 15) may be regarded as preventable deaths in patients whose general condition and lack of other pathologic changes made them salvageable. Five cases (cases 5, 6, 9, 10, 11) seem neither salvageable nor preventable; the remaining three were either non-preventable or non-salvageable.

Of the eight deaths in category 2 (acute perforation), four (cases 18, 19, 22 and 23) were salvageable and preventable, viewed in retrospect. Case 16 was neither salvageable nor preventable. Cases 17 and 20 were probably preventable but not clearly salvageable. Case 21 was salvageable, but because of lack of ulcer history, hardly preventable. These terms (preventable, salvage-

able) refer to the *history*, not to the immediate surgical problem of treating the perforation.

Thus of 23 deaths in the 808 classified patients who received no definitive surgery at the Massachusetts General Hospital in 1942–1946 (categories 1 and 2), 11 were pathologically salvageable and clinically preventable by proceeding with earlier definitive surgery, which with its inherent risk of 2.86 per cent would have claimed one patient or less of these 11 patients (on a statistical expectancy basis). Six of these patients (cases 1, 2, 3, 8, 13 and 15) had previous serious complications or previous Massachusetts General Hospital admissions to give additional warning of the presence of a progressive and virulent form of the disease. The other 12 deaths must be viewed as having clinical features making rescue unlikely or excessively hazardous.

All five deaths following subtotal gastrectomy were truly surgical deaths tactically salvageable if all details of the postoperative course had proceeded according to plan; there were no patients of such advanced age and infirmity that the surgeon could claim "calculated risk" or make out a case for surgery as a desperate measure for a patient in *extremis*. All five were both salvageable and preventable, viewed in the framework used in the foregoing paragraphs. Two of the five (cases 27 and 28) had such long and complicated histories that surgical approach at a younger age and with less advanced local pathology might have been expected to carry a lesser risk.

There were no vagotomy ulcer deaths.

The lack of late ulcer deaths in the category 3 and 4 cases (the 189 gastrectomies and vagotomies) is probably not significant, since time enough has not elapsed since operation.

PATTERNS OF FAILURE SHORT OF FATALITY

Although the 28 ulcer deaths in the series form a highly significant group, they do not have the statistical importance of those classified as Class IV (Poor) Results which include 28.6 per cent of the entire group of traced patients (285 individuals). An analysis of the reasons why these patients were classified as failures may lead us to a better understanding of the phenomena involved in the natural history of progressive duodenal ulcer disease. These will also be dealt with according to categories of treatment (Table III).

Category 1.—Patients in whom no definitive surgery was performed at the Massachusetts General Hospital, 1942–1946 (738 cases classified):

In the non-surgical group, 96 (13 per cent) were classified as poor results because of subsequent major complications or surgery (IV c); 79 (11 per cent) because of economic incapacity (IV e) (loss of more than 14 days in the past year because of ulcer difficulty) and 51 (7 per cent) were "dissatisfied for other reasons" (IV g). It will be profitable to examine these subcategories of poor results more closely.

1-IV c. There are 96 patients in category 1 who were classified as having a poor result because of subsequent major ulcer complications or surgery. Of

these, 25 had subsequent major hemorrhages, most of them treated in other hospitals. Six had subsequent perforations. A total of 58 had subsequent major surgery for their ulcers (definitive surgery) or for the complications of ulcer. Most of these definitive operations and ulcer complications requiring surgery occurred at outside hospitals, a few of them occurred at the Massachusetts General Hospital after 1946. The remaining seven patients had other major ulcer difficulties, including prolonged intractable pain and symptoms of obstruction. These 96 patients, then, had unequivocal evidence of failure of the regimen instituted.

1-IV e. There were 79 patients in category 1 who were classified as poor results because of economic handicap. Of these, 14 lost eight to 20 days' work,

TABLE III.—*Duodenal Ulcer, 1942–1946, Subclassification of Poor Results (Class IV).*

Category	Number Classified	Class IV* IV a	IV b	IV c	IV d	IV e	IV f	IV g	Total IV
1 Non-surgical	738	0	15 2%	96 13%	0	79 11%	0	51 7%	241 32.6%
2 Perforating	70	5 7%	3 4%	6 9%	0	2 3%	0	3 4%	19 27.1%
3 Subtotal gastrectomy	155	5 3%†	0	5 3%	3 2%	0	3 2%	3 2%	19 12.3%
4 Vagus resection	34	0	0	6 18%	0	0	0	0	6 17.7%
Totals	997	10 1%	18 1.9%	113 11%	3 0.3%	81 8%	3 0.3%	57 6%	285 28.6%

* Class IV is sub-classified as follows:
a — Postoperative death.
b — Ulcer death.
c — Major ulcer complication or subsequent definitive surgery.
d — Severely underweight.
e — Economic incapacity.
f — Persistent disability as side-effect of treatment.
g — Poor result for other reasons.

† The postoperative mortality in the 175 sub-total gastrectomies was 2.86 per cent (5 deaths in 175 resections).

28 lost 21 to 40 days' work and 37 lost over 41 days' work in the year prior to our most recent follow-up contact.

1-IV g. There were 50 patients in category 1 who were classified as poor results because of "other reasons." This polyglot group is best illustrated by a few examples:

Patient H., 131,186, was treated in the Out-Patient Department for duodenal ulcer in 1943 and has been seen at intervals since that time. He has occasional vomiting spells, lost eight days' work in the year prior to his questionnaire, and states that he is worse off than when first seen in the hospital.

Patient C., 444,457, a 44-year-old male, was first seen in the Massachusetts General Hospital, Out-Patient Department in 1944. He was placed on an ulcer regimen and has been followed since. He continues to have ulcer symptoms, lost time from work in 1948 because of them, and has an active ulcer crater on his last roentgen ray examination.

Patient Z., 349,200, a 39-year-old male first seen in 1946, continued to have symptoms on a good diet. He has had a recent hemorrhage and lost eight days' work in 1948.

Of the 738 patients in category 1, 329 or 44.6 per cent were hospitalized for ulcer on the wards of the hospital, and 409 (55.4 per cent) were treated only in the Out-Patient Department. The effect of this difference on results is not dramatic. The out-patients had a slightly lower incidence of failure than the house cases (29.1 per cent Class IV results as versus 37.1 per cent in the house cases) and a slightly higher incidence of excellent (Class I) results (16.4 per cent as versus 13.4 per cent). These minor differences might be predicted on the basis of the fact that the more severe cases are admitted to the hospital.

Category 2.—Patients who were treated at the Massachusetts General Hospital, 1942–1946, for acute perforation (70 classified cases):

In this group six patients (9 per cent) were classified as having a poor result because of subsequent major ulcer complications or surgery (2-IV c). Of these six patients, four had definitive surgery carried out later at an outside hospital, one re-perforated and one developed large painful hernias after two drainages of subhepatic abscess. Eight died of their perforation as recounted previously.

There were five other patients in category 2 who had poor results for a miscellany of reasons, including economic incapacity and dissatisfaction of the patient with his ulcer symptoms.

Category 3—Patients who had subtotal gastrectomy at the Massachusetts General Hospital, 1942–1946, (155 classified cases):

There are five patients in the gastrectomy group to whom poor results were assigned because of later major ulcer complications or surgery (3-IV c). Three of these patients developed proved jejunal ulcer and two had symptoms compatible with jejunal ulcer, a total incidence of five in the 155 followed cases (3 per cent). One case, N. S. (341,839), bled six years postoperatively and jejunal ulcer was proved by roentgen ray. Patient W. W., (320,712), perforated a stomal ulcer one year postoperatively and had a vagus resection carried out in another hospital. Patient H. D. (27,407), developed a stomal ulcer one year after a resection, had a re-resection and has been well since. J. S. (267,405), perforated an anastomotic ulcer two months after his resection and has been well since without management. Patient A. V. (427,309), bled massively two years after his resection, presumably from a jejunal ulcer, the presence of which was never established.

Three patients belong in category 3-IV d because of failure due to chronic malnourishment after subtotal gastrectomy. Two patients are underweight, (25 and 30 pounds respectively), one remained malnourished, required revision of his stoma, and died seven years later of pulmonary tuberculosis. There are no poor results due only to economic handicap (3-IV e) after resection.

Three patients after subtotal gastrectomy belong in the group of failures due to untoward side-effects (3-IV f). Of these, one had weakness in his legs

beginning two months after spinal anesthesia and persisting to follow-up five years later, one had a severe "dumping syndrome," not well controlled and causing periodic illness. One patient has a "dumping syndrome," well controlled by careful diet. This leaves us with an incidence of very severe "dumping syndrome" of about 1.6 per cent. It should be emphasized that this figure only includes patients in whom the "dumping syndrome" was of serious and continuing disabling significance. It has been our experience that symptoms characteristic of the "dumping syndrome"* occur transiently at some time after operation in about 30 per cent of individuals having subtotal gastrectomy if they are closely questioned.

The miscellaneous group of failures has three members from the resected patients as follows:

Patient E. (455,785), had a subtotal resection in 1944. He now has an incisional hernia which has not been repaired and which gives him symptoms.

Patient G. (257,637), a 57-year-old male, reports constant pain which requires the attention of his family physician. He is not working and has lost 10 pounds in weight.

Patient K., (12,449), is a 63-year-old man who was operated upon in 1945. He continues to report abdominal pain and has failed to regain normal weight.

Category 4—Patients undergoing vagus resection at the Massachusetts General Hospital, 1942–1946, (34 cases):

There were six failures in the vagus group, all of them falling into that classification assigned to major ulcer complications or surgery (4-IV c).

Patient G. B. (270,852), developed a recurrent ulcer crater about two years after vagotomy; he persistently denied symptoms but progressively lost weight. About a year later he developed a pulmonary carcinoma to which he subsequently succumbed.

Patient M. E. (433,311), was a patient with Raynaud's disease, esophageal ulcer, and duodenal ulcer. Four years following transthoracic vagotomy, she developed renewed esophageal and duodenal ulceration with obstruction at the lower end of the esophagus, requiring bouginage.

Patient J. P. (501,746), had had a subtotal gastrectomy at another hospital in which the antrum of the stomach was left in place (the "antral syndrome"). A vagotomy was carried out with the hope that the vagus governs the secretory function of the antral mucous membrane. This was not the case and removal of the retained gastric antrum was necessary to achieve healing. Strictly speaking, this is hardly a failure of vagotomy alone since it also involves an inadequate subtotal gastrectomy. Yet, by our criteria, as a patient undergoing vagotomy at the Massachusetts General Hospital in 1942–1946, subsequent major surgery was required and, therefore, the patient stands as a class 4-IV c failure.

Patient J. S. (413,140), required a subtotal gastrectomy two years after vagotomy for duodenal ulcer because of the presence of a large gastric ulcer.

* The term "dumping syndrome" is used quite specifically here to denote a feeling of faintness and warmth coming on soon after eating, with flushing, palpitation, varying degrees of abdominal pain and a desire to lie down. Other types of postprandial symptoms are not included; in case the incidence of dumping syndrome here seems low it should be pointed out that 10 of the 18 Class III results after subtotal gastrectomy were assigned because of dumping syndrome severe enough to give an "unsatisfactory" result but not severe enough to be assigned as a "poor" (Class IV) result.

Patient J. V. (456,917), required a subtotal gastrectomy two and a half years after vagotomy because of obstructive symptoms, markedly delayed gastric emptying and malnutrition.

Patient M. McN. (344,702), required a subtotal gastrectomy about three years after vagotomy because of a recurrent duodenal ulcer complicating her chronic diarrhea. It is of interest that this patient had a flat insulin test at this time, an experience which has been noteworthy in several other recurrent ulcers after vagotomy.

There were no vagotomy failures in any of the other subclassifications of Class IV.

Discussion of Failures. In the deaths previously noted, two distinct patterns were discernible, (1) the "preventable deaths" where readier recourse to definitive surgery resulting from a more realistic evaluation of the cause of progressive duodenal ulcer might have been helpful and (2) those non-preventable or non-salvageable deaths in which little forewarning was given of a fatal turn of duodenal ulcer disease, or where concomitant renal or cardiac disease made rescue impossible.

The pattern of failure short of fatality is in contrast quite consistent. The failures are all essentially the same whether the patient has had surgery or not. The only difference to be discerned is that there are about twice as many failures in the non-surgical group as in the surgical group. The outstanding failures in all instances are those described as class IV c, meaning subsequent major ulcer complications, or deterioration requiring definitive surgery.

This calls to mind the essential unity of duodenal ulcer disease. A spectrum of therapy ranging on the one hand from simple diet or the most casual type of conversational management to, on the other hand, extensive consultation by specialists, psychiatry and definitive surgery, has a pattern of failure which is the same throughout. This pattern is characterized by recurrence not only of the ulcer by roentgen ray but of the organic changes which the disease induces, culminating in hemorrhage, perforation, painful ulceration or obstruction. It is in this category also that vagotomy has its most egregious failure. Indeed, the percentage of class IV c results is higher in vagotomy than in any other group in the whole series, suggesting that the operation of vagotomy, whatever its other effects, certainly has not altered the essential characteristic of this disease, namely that of recurrence with anatomic complications due to digestion of tissue in the upper gastro-intestinal tract.

The predominant pattern of failure due to subsequent major ulcer complications, major ulcer surgery or complications of ulcer surgery, is broken at one point in the medical series. This alteration in pattern arises from the 11 per cent incidence of economic incapacity as a cause of failure in the non-surgically treated group. Although definitive surgery has in general the same type of failure shown by medical treatment, it has these failures at a much lower rate of incidence and is noteworthy because economic incapacity is practically removed from the scene.

PERFORATION

We are examining the history of a benign process whose most outstanding local anatomic characteristic is the digestion of tissue. It is therefore of interest to separate out from the group those cases where this digestion has occurred so rapidly and to such depth as to produce a free perforation into the peritoneal cavity. We may then discern whether or not this group of patients has any different make-up or any different prognostic significance from the rest of the patients.

TABLE IV.—*Duodenal Ulcer, 1942–1946, Incidence of Perforation.*

Classified patients		997
Previous perforations	62	
Acute perforations	70	
Subsequent perforations	14	
Total perforations	146	(14.7%)

Incidence of Perforation. Of the 1246 patients whose records were abstracted, a total of 151 or 12 per cent had perforated sometime prior to admission to the Massachusetts General Hospital, but only 85 or 6.8 per cent presented the problem of acute perforation and were treated specifically for this perforation. Of this group of 85, two had previous perforations to their credit.

TABLE V.—*Duodenal Ulcer, 1942–1946, Subsequent Fate of Patients Suffering Perforation.*

A. Acute perforation	62 Survivors traced	
Satisfactory (Class I and II)	34 (54.7%)	
Unsatisfactory (Class III and IV)	28 (45.3%)	
Poor results (Class IV)		11 (17.8%)
B. Previous perforation with present symptoms	62 Traced	
Satisfactory (Class I and II)	9 (14.5%)	
Unsatisfactory (Class III and IV)	53 (85.5%)	
Poor results (Class IV)		51 (82.2%)
Dead of ulcer: 4.		
Subsequent definitive surgery: 37.		
Re-perforation: 2		
Other types of failure: 8.		

Of the 997 patients followed and classified, 62 had previous perforations, 70 had acute perforations and 14 had perforations after their 1942–1946 episode, giving an over-all figure of 14.7 per cent as a first approximation for the incidence of perforation in the total time span studied. Several had multiple perforations (Table IV).

Fate of Perforators. It has become evident that the prognosis following a single perforation is far better than that for a patient with perforation in the past who re-enters with renewed symptoms (Table V). Of 62 traced survivors of acute perforation at the Massachusetts General Hospital 1942–1946,

34 (54.7 per cent) went on to satisfactory results, and only 11 (17.8 per cent) had failures.

In contrast, the 62 traced patients with previous perforation and renewed symptoms showed only nine satisfactory courses (14.5 per cent) and 51 (82.2 per cent) failures of non-surgical management. Of these 51 failures, four died later of ulcer, 37 required definitive surgery and two re-perforated. This difference in failure rate is strongly significant with a probability ratio of 9.26.

It would appear from this that perforation may literally be a "meaningless accident" in duodenal ulcer disease; a recurrence of symptoms guarantees that it was no such accident.

The total mortality of perforation is impressive. Of 132 patients with past or present perforation who were classified, 12 died at the time of perforation or later from duodenal ulcer or its complications, a mortality of 9.1 per cent.

Of the 25 patients in category 1 (non-surgical treatment) who had previous perforations and who were followed up to classification, four or 16 per cent are now dead of ulcers and 12 or 48 per cent have had poor results. Of the 15 patients in the non-surgical group who died of ulcer or its complications, perforation played a role in the fatality of eight or 53 per cent. Four of the patients in category 1 who previously perforated (16 per cent) have had subsequent definitive surgery.

In category 3, the subtotal gastrectomies, 29 patients (16.5 per cent) had a history of previous perforation. There were no deaths in those patients who had had previous perforations, a striking contrast to the 16 per cent mortality in previously perforated patients who had no definitive surgery. Of these 29 cases with previous perforations who came to subtotal gastrectomy five had a poor (Class IV) result.

These data on perforation point to the fact that when perforation is later followed by relapse it leads to fatality, re-perforation, obstruction, lasting symptoms and the necessity for subsequent definitive surgery in a higher percentage of cases than in any other sub-group studied.

Perforation has often been considered as an acute problem, as a surgical emergency in which tactics are of importance only in producing survival. In addition, perforation may be an event in the life history of ulcer which should alter our strategy; if followed by even a single relapse it denotes a virulent form of the disease and unless dealt with by definitive surgery bodes ill for the prognosis of the patient. Perforation may come out of a clear sky and the sky may remain clear thereafter; when the sky does not remain clear thereafter, a very bad storm is brewing.

HEMORRHAGE

The incidence and prognostic significance of hemorrhage are a great deal more difficult to quantitate than is the case with perforation. Perforation is an "all or none" phenomenon, an indubitable event in the patient's history not subject to quantitative variation. Hemorrhage by contrast varies from a single

tarry stool to an exsanguinating hematemesis or melena. It would be valid to expect all duodenal ulcer patients to have occult blood in the feces on at least one occasion, when duodenal ulceration is actively occurring; hemorrhage is accordingly somewhat more common than perforation. An attempt to compare hemorrhage with perforation as a determinant of subsequent course has yielded the following facts:

Incidence of Hemorrhage. Of the 997 classified patients, 229 or 23 per cent had a history of previous hemorrhage of sufficient significance to play a prominent part in the history. Multiple previous hemorrhages were by no means rare.

Deaths from acute massive hemorrhage in the whole group were eight (cases 3, 6, 9, 10, 11, 12, 14, 25) of which seven were in the non-surgical category and one (case 25) was treated by subtotal gastrectomy.

Thirty-seven patients had subsequent hemorrhage serious enough to warrant a Poor classification on that account. This yields an overall figure of 274 cases or a 27.5 per cent incidence of significant hemorrhage, twice the 13.5 per cent incidence of perforation.

Fate of Bleeders. Of this entire group of 274, eight are now dead of hemorrhage and seven who had previous hemorrhage of significance in the history are dead of ulcer (cases 1, 2, 8, 17, 23, 27, 28) by mechanisms other than hemorrhage. This yields a mortality of 5.5 per cent, somewhat less than the ulcer mortality in patients with perforation as a feature in the history (9.1 per cent).

Of the 177 classified patients in category 1 (non-surgical) who had hemorrhage as a prominent symptom in history, 64 or 36 per cent have Poor results as contrasted with the 48 per cent Poor results in the small group of 25 non-surgically treated "previous perforators." The recurrent tendency of hemorrhage is much more striking than perforation. It will be recalled that two of the 85 acute perforators had previously perforated, and that two of the Poor results were due to reperforation. In contrast, of the 177 classified patients in category 1 with *previous hemorrhage*, 23 (13 per cent) were classified as poor results because of subsequent non-fatal hemorrhages and eight (4.5 per cent) are dead of hemorrhage. Of the 554 classified patients in category 1, with *no previous hemorrhage*, only 12 (2.16 per cent) were classified as Poor results because of subsequent hemorrhage and only four (0.73 per cent) died of hemorrhage.

In the subtotal gastrectomy cases hemorrhage played a role in the indication for surgery in 41 or 23.5 per cent. Of these 41 cases, one (case 25) died postoperatively and three others have Poor results, a total incidence of failure of 10 per cent.

Eleven of the 34 vagotomy patients had previous hemorrhages; none was operated upon for acute massive hemorrhage and none of these 11 had subsequent hemorrhages or class IV results—seemingly a category in which vagotomy was quite effective, although numbers are small.

"Significant hemorrhage" has been loosely applied here and means hemorrhage noticeable enough to be a distinct historical episode to the patient. This seems a reasonable definition for our present purpose, which is specifically to find clues as to ulcer prognosis. Used in this sense, hemorrhage is not as grave a prognostic index for failure or fatality as a perforation followed by ulcer symptoms. All will agree that acute massive hemorrhage in elderly individuals is peculiarly lethal as an ulcer complication and indeed our death list supports such a contention. Taking all hemorrhages rather than this one

TABLE VI.—*Duodenal Ulcer, 1942–1946, Sex Factors in Result.*

Category	Sex	Number Classified	Class I Excellent		Class II Good		Class III Fair		Class IV Poor	
1 and 2 Non-surgical	M	628	102	16.2%	181	28.8%	118	18.8%	227	36.2%
1 and 2 Non-surgical	F	180	25	13.9%	60	33.4%	62	34.4%	33	18.3%
3 and 4 Def. surgery	M	166	80	48.3%	48	28.9%	16	9.6%	22	13.2%
3 and 4 Def. surgery	F	23	11	47.8%	5	21.8%	4	17.4%	3	13.0%
Total	M	794	182	22.9%	229	28.8%	134	16.9%	249	31.4%
Total	F	203	36	17.7%	65	32.0%	66	32.5%	36	17.8%
Total		997	218	21.9%	294	29.5%	200	20.0%	285	28.6%

unfavorable group, the long-term outlook is not quite as poor as with past perforation and present symptoms. Perforation is less common than hemorrhage, but if followed by renewed symptoms it is a more certain index of "virulence" of the ulcer process.

OTHER CORRELATIVE FACTORS

Sex. The largest difference between the two sex groups appears in the mortality rate. Although males outnumber females by more than four to one (1004–242) in the entire series, the difference in ulcer mortality was in the proportion of seven to one (3.4 per cent death rate in males, 27 in 794 males; 0.5 per cent death rate in females, one in 203 females). Another striking disparity is in the uneven distribution of the fair and poor results. Although the division of unsatisfactory results (fair or poor) was nearly identical, males had about twice as many poor and about half as many fair results as did females (Table VI).

Age of onset. The age of onset of symptoms was analyzed in this group of patients, but the results were not rewarding (Tables VII-A and VII-B). The age of onset appears to make surprisingly little difference with the possible exception of a tendency towards poorer results in the patients whose symptoms began before the age of 20 or after the age of 65. As is clear from the death list, there is a group of men who acquire a duodenal ulcer when of advanced age. They have a very poor prognosis because of their age and general condition.

Duration of History. The duration of ulcer history as measured from the onset of ulcer symptoms to the date of the follow-up observations is known in 945 cases (Table VIII). The death rate of 13.9 per cent for the ulcers of shortest duration is very interesting. This is given additional meaning when

TABLE VII-A.—*Duodenal Ulcer, 1942–1946, Effect of Onset Age on Result Achieved in Patients Without Definitive Surgery (Categories 1 & 2).*

Onset Age	Number Classified	Result: Class I Excellent	Class II Good	Class III Fair	Class IV Poor
10–20 years	58	10 17.2%	12 20.7%	14 24.1%	22 38.0%
21–30 years	158	19 12.0%	53 33.5%	28 17.7%	58 36.8%
31–40 years	209	28 13.4%	56 26.8%	55 26.3%	70 33.5%
41–50 years	165	24 14.5%	50 30.3%	34 20.6%	57 34.6%
51 and over	154	39 25.3%	52 33.7%	28 18.2%	35 22.8%

it is pointed out that these highly fatal ulcers of short duration are in old individuals who represent the group mentioned in the above paragraph. The consistent similarity of incidence of poor result (medical or surgical) regardless of duration of ulcer history in patients under 65 is quite clearcut.

TABLE VII-B.—*Duodenal Ulcer, 1942–1946, Effect of Onset Age on Result Achieved in Patients With Subtotal Gastrectomy (Category 3).*

Onset Age	Number Classified	Result: Class I Excellent	Class II Good	Class III Fair	Class IV Poor
10–20 years	22	11 50.0%	5 22.8%	3 13.6%	3 13.6%
21–30 years	36	20 55.6%	8 22.2%	4 11.1%	4 11.1%
31–40 years	33	18 54.6%	8 24.2%	4 12.1%	3 9.1%
1–50 years	37	19 51.5%	7 18.9%	5 13.5%	6 16.1%
1 and over	26	15 57.7%	7 27.0%	1 3.8%	3 11.5%

DEFINITIVE SURGERY

The nature and results of definitive surgery carried out at the Massachusetts General Hospital in 1942–1946 have been dealt with in other sections and will not be reviewed here. The definitive surgery carried out elsewhere or outside the 1942–1946 limit of classification will be mentioned briefly (Tables IX and X).

Previous Definitive Surgery. Of the 952 Category 1 (non-surgically treated) patients whose records were abstracted, 15 had previous posterior gastro-enterostomies, an incidence of 1.6 per cent previous attempts at definitive surgery by technical means now regarded as inadequate save in exceptional circumstances.

None of the acute perforating ulcers had previous definitive surgery.

Previously attempted definitive surgery characterized the history of 20 (11.4 per cent) of those patients undergoing subtotal gastrectomy at the Massachusetts General Hospital 1942–1946. Of these, the majority (16) were posterior gastro-enterostomies, the remainder divided between pyloroplasty (2) and subtotal gastrectomy (2).

In the vagotomy group five patients had previous definitive surgery (three gastrectomies, two gastro-enterostomies).

TABLE VIII.—*Duodenal Ulcer, 1942–1946, Effect of Duration of Symptoms on Mortality Rate in 945 Classified Cases Regardless of Treatment.*

Duration	Number Classified	Ulcer Deaths No.	%
Under 2 years	72	10	13.9%
2 to 5 years	284	3	1.1%
6 to 10 years	318	8	2.5%
11 to 20 years	188	2	1.1%
Over 20 years	83	3	3.6%
Total	945	26	2.7%

Thus in 3.2 per cent of the 1246 records was there evidence of a previous operation planned to cure the patient. Many of these had failed by the criteria used herein. As pointed out in the section on "Materials and Methods," our effort has not been to classify previous treatment or treatment in other hospitals, and for this reason the failures of previous medical treatment and of these 40 previous surgical operations do not so appear in the results: they are a part of the history, not a feature of the treatment we are examining.

TABLE IX.—*Duodenal Ulcer, 1942–1946, Incidence of Previous Definitive Surgery.*

	Category	Number Abstracted	Previous Definitive Surgery: Pyloroplasty	Gastro-enterostomy	Gastrectomy	Total	%
1	Non-surgical	952	0	15	0	15	1.6%
2	Perforating	85	0	0	0	0	0.0%
3	Subtotal gastrectomy	175	2	16	2	20	11.4%
4	Vagus resection	34	0	2	3	5	14.7%
	Totals	1246	2	33*	5*	40	3.2%

* In these 38 cases jejunal ulcer was present or suspected at the first Massachusetts General Hospital Admission.

In the 997 classified cases there were 18 instances where posterior gastro-enterostomy was followed later by subtotal gastrectomy for jejunal ulcer. The length of time intervening between the posterior gastro-enterostomy and the development of symptoms of jejunal ulcer (duration of relief from posterior gastro-enterostomy) shows two patterns. One-half the cases had relief ranging from zero to three years (average 1–3/12 years); the other half ranged from

three to 23 years (average 11–5/12 years with six cases over ten years of relief).

Subsequent Definitive Surgery. Subsequent to the 1942–1946 episode at the Massachusetts General Hospital there were 67 definitive surgical operations, all of which constitute *prima facie* evidence of failure of the 1942–1946 treatment (whether medical or surgical) by definition of Class IV c (poor result due to necessity for subsequent definitive surgery).

Of those subsequent operations, 14 were carried out at the Massachusetts General Hospital after 1946, 53 at outside hospitals. It is clear that a research method confined to record analysis would have overlooked 80 per cent of the subsequent surgery.

Five of the subsequent 67 operations were carried out on patients treated by definitive surgery at the Massachusetts General Hospital, 1942–1946. Two of the gastrectomies had to be re-operated upon (one by re-resection and one

TABLE X.—*Duodenal Ulcer, 1942–1946, Incidence of Definitive Surgery Subsequent to Admission in Classified Patients.*

	Category	Number Classified	Def. Surg. M.G.H. '42-'46	Definitive Surgery Subsequent to Discharge							
				M.G.H.		At Other Hospitals					
				Stg.	Pge.	Stg.	Pge.	Vagus	Unknown	Total	%
1	Non-surgical	738	0	10	1	34	5	6	2	58	7.9%
2	Perforating	70	0	1	0	1	1	1	0	4	5.7%
3	Subtotal gastrectomy	155	155	0	0	1	0	1	0	2	1.3%
4	Vagus resection	34	34	2	0	1	0	0	0	3	8.8%
	Totals	997	189	13	1	37	6	8	2	67	6.8%

Total definitive surgery at Massachusetts General Hospital, 204 (20.4%).
Total definitive surgery at other hospitals subsequent to M G.H. admission, 53 (5.3%).
Total definitive surgery subsequent to M.G.H. admission, 256 (25.7%).
Per cent of definitive surgery carried out elsewhere, 20.6%.

by vagotomy); three of the vagotomies required re-operation, all by gastrectomy.

The remaining 62 operations were carried out on patients who received no definitive surgery at the Massachusetts General Hospital, 1942–1946, 58 in the category 1 patients and four in patients who perforated just prior to their Massachusetts General Hospital admission. In all these instances the progressing ulcer process required surgery despite attempts to control the situation non-surgically; this further event in the history of the disease took place at the Massachusetts General Hospital in 12 cases, elsewhere in 50.

In summary, of the 1246 patients whose records were abstracted, 40 had had previous definitive surgery; 189 had surgery at the Massachusetts General Hospital, 1942–1946; of the 997 classified patients, 67 had subsequent definitive surgery. *Leaving out repeated operations on the same individuals,* the total incidence of definitive surgery in the group studied is about 25 per

cent. This figure is a first approximation because of the heterogeneous group from which the percentages are taken. It is probably accurate to state that between 24 and 26 per cent of these patients had at one time or another up to completion of follow-up an attempted definitive operation.

DISCUSSION

Despite the unity of ulcer disease as demonstrated by the patterns of failure, there is clearly a spread in the intensity with which this disease may occur in individual patients. Certain evidences may suggest that the disease is capable of rapid and penetrating tissue digestion. Chief among these are perforation and bleeding. Persistent severe pain is apparently a manifestation of this progression, although more difficult to define statistically. The consistently better results obtained by subtotal gastrectomy and the lack of late ulcer deaths in those operated on in the Massachusetts General Hospital, 1942–1946, would argue strongly for the performance of this operation as soon as progressive ulcer disease can be diagnosed. Before embracing this conclusion wholeheartedly, we must point out that the subtotal gastrectomy group consisted largely of middle-aged patients, and that another ten or 20 years must pass before we can state that they have had a lower incidence of late ulcer deaths than the non-surgical patients. There is no question about their greatly improved results in terms of medical and economic rehabilitation; no further time is needed to establish a significant percentile difference here.

In reviewing the non-surgically treated patients, one is impressed by the large number of individuals who have ulcer symptoms on one or two occasions, sometimes even with hospital admissions, but who then undergo some change —organic, psychiatric, or environmental—which holds the ulcer diathesis in check for many years. It is significant that this benign form of the disease occurs much less commonly when a past perforation is followed by renewed symptoms, when hemorrhage is part of the history, when pain is not amenable to management and when onset is at the extremes of life. Males are universally less fortunate than females in this regard. When these ill omens are present we should make a new diagnosis, that of "progressive" or "virulent" ulcer disease. This diagnosis places the patient in the worst prognostic group of duodenal ulcer and serves as a guide to treatment.

In treating such a patient, definitive surgery appears about twice as likely to give a good result as does avoidance of that surgery; his likelihood of dying from ulcer has apparently diminished if he is given definitive surgery.

The patient with a recurrent ulcer without hemorrhage or perforation but with recurrent pain is the most difficult to classify. Whether he should or should not have definitive surgery is difficult to state categorically and most surgical pronouncements have been conservative on this score. Control of ulcer symptoms on "ideal hospital management" is useful diagnostically and as a preparation for surgery but has been a false idol in non-surgical management. The fact that a patient is well handled by the practice of physic on a

hospital ward does not signify satisfactory management when the same patient returns to home, family and business. He must live his life among the latter and it is to symptom-freedom in that environment that attention should be directed. If it cannot be secured in a reasonable time, surgery should be undertaken.

It should be mentioned that obstruction does not acquire much if any importance in this study. Obstruction due to "spasm" or "edema" is a symptom of acute activity. Cicatricial obstruction is a late result of an old organic disease and it has little prognostic significance since it is occurring at the end of the life history of a disease and in itself requires relief, wholly aside from any remaining ulcer activity. There have been no patients with persistent obstruction successfully carried on medical measures; this was attempted in some cases, the physicians being unaware of the continued presence of partial obstruction.

Finally, we would do well to omit the "intractable ulcer" from our vocabulary. What is meant is that the patient's disease is of the "progressive," or "virulent" variety, a diagnosis which can often be made long before enough therapeutic failures have accumulated to justify the term "intractable." The nicety of ulcer care in future years lies in the diagnosis of progressive or virulent ulcer disease and its appropriate treatment before failure has occurred to an extent which justifies the use of the term "intractable." At the time of this writing there is nothing to offer the patient that is effective, yet less radical than subtotal gastrectomy. More evidence by careful comparative follow-up must be accumulated on patients undergoing vagotomy or vagotomy with anastomotic combinations, before we can confidently eliminate gastrectomy as the most effective form of definitive treatment for progressive virulent duodenal ulcer.

FORMULATION

I. On the basis of these data it is possible to advance a set of primary and secondary criteria for the diagnosis of progressive or virulent ulcer disease:

A—Primary criteria

1. One perforation in the past, with present ulcer symptoms.
2. One acute hemorrhage requiring blood transfusion.
3. Progressive pain over a two-year period under a physician's care and advice in the patient's normal living environment, at work.

B—Secondary criteria

1. A male with duodenal ulcer symptoms under a physician's care.
2. A male with onset of symptoms prior to the age of 20 or subsequent to the age of 65.

II. If two of these criteria, at least one of which must be primary, are present, the diagnosis of progressive virulent ulcer disease may be considered established.

III. Once established, the outlook for a satisfactory result on non-surgical management is poor and the intrinsic mortality elevated.

IV. If surgical skill and facilities are available for accomplishing subtotal gastrectomy with a low mortality, the patient should be offered this procedure.

V. If three criteria are present, such surgery should be urged. Symptomatic alleviation under hospital conditions does not alter the importance of these criteria. Obstruction is an end-stage in the natural history of ulcer, and in itself requires operation for relief; it therefore does not appear amongst these diagnostic criteria.

VI—If subtotal gastrectomy cannot be safely accomplished under the conditions available, we have no irrefutable evidence that other operations can replace it.

SUMMARY

1. The records of all the duodenal ulcer patients managed with or without surgery at the Massachusetts General Hospital during the years 1942–1946 have been abstracted and reviewed; 1246 such records were reviewed.

2. Nine hundred and ninety-seven of these patients have been followed to mid-1949 and enough data collected to form a valid clinical judgment as to the success of their regimens in 1942–1946 and thereafter.

3. These results have been classified by the same criteria whether the technics and skills of medicine or surgery formed the predominant feature in the management of the patient.

4. The concept of "progressive" or "virulent" duodenal ulcer disease emerges as expressing the outstanding feature of that fraction of the ulcer population who do poorly without definitive surgery.

5. The occurrence of a past perforation with present symptoms, an acute hemorrhage, progressive pain under a physician's care at home, or onset at the extremes of life in male patients are clues to this diagnosis.

6. The mortality from hemorrhage, perforation and late obstruction in non-operated patients appears to balance the intrinsic hospital mortality of definitive surgery.

7. Following definitive surgery only half as many patients have an unsatisfactory result in symptomatic or economic terms as do those managed without surgery.

8. One is led therefore to the conclusion that the diagnosis of "duodenal ulcer" is not enough. Once this general classification is made by the usual methods, the doctor must proceed to the consideration of a more important diagnosis: "progressive virulent ulcer disease."

9. When established, the diagnosis of progressive virulent ulcer disease is the key to the prognosis; a definite decision as to surgery should be made. Our data indicate that subtotal gastrectomy should be undertaken.

10. Such a conclusion can be acted upon conscientiously only when the surgical skill and facilities are available to permit performance of subtotal

gastrectomy with an acceptable mortality. A policy for each hospital can only be made after critical study of its own cases.

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THE DEFINITIVE TREATMENT OF BLEEDING PEPTIC ULCER*

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DURING THE LAST FOUR YEARS we have been testing the value of immediate blood replacement and gastric resection in patients with acute massive gastroduodenal bleeding diagnosed as being due to peptic ulcer. By the term "acute" we mean that the patient has shown gross evidence of bleeding within one week, and by the term "massive" bleeding, we mean bleeding of such severity as to lower the total circulating red cell mass to less than 60 per cent of normal. Patients who met these criteria but preferred nonsurgical treatment served as controls. Our experience now comprises 65 cases in the operative group with seven deaths (10.7 per cent) and 42 cases in the nonoperative group with nine deaths (21.4 per cent).

In previous reports, we have presented preliminary and tentative evaluation of our data.[1, 2] As the work has progressed, we have become convinced that massive bleeding from peptic ulcer is not uncommon, that it is life-endangering, and that it must be regarded as amenable to surgical arrest. Referring physicians evidently are coming to share our viewpoint, for fewer and fewer cases are available to us for control study without operation. The present report, therefore, deals with the last 50 consecutive cases treated by blood replacement and early operation, and consists of a clinical analysis of this experience. The mortality rate for the group was 6 per cent.

The method of handling these cases may be briefly described. On admission of a suspected case of acute gastroduodenal bleeding to the hospital, the resident and laboratory teams are immediately called. Blood studies are made within a half-hour, including the all-important measurement of total circulating red cell mass, as well as determinations to exclude hemorrhagic diathesis and primary blood diseases. As a part of the study also, plasma samples are taken for analysis of sodium, potassium, protein and non-protein nitrogen concentrations. After the initial blood samples are taken, transfusions are started in one or more veins, and the findings of the history and physical examination are checked. A nasogastric tube is placed and the gastric contents are examined for blood and acid. If a presumptive diagnosis of bleeding peptic ulcer is made and the criteria as to acuteness and severity of hemorrhage are met, laparotomy is begun without further delay, regardless of what the blood pressure reading may be and regardless of whether the patient may appear to be

* Read before the American Surgical Association, Colorado Springs, Colo., April 20, 1950. The laboratory aspects of this study were supported by a grant from the Veterans Administration.

bleeding actively at the moment. At least three liters of properly matched blood must be on hand, however, and as anesthesia is begun, the rate of administration of blood is rapidly increased.

A few general remarks about this group of 50 patients are in order. For the most part, as shown in Table I, they were older patients with considerable associated disease. Nineteen patients, or 38 per cent, were in obvious hemorrhagic shock on arrival at the hospital. Forty-one patients, or 82 per cent, had recently vomited blood. Forty-two were males and eight females. With respect to history, the patients fell into two groups. Three-quarters of the patients had a long history of peptic ulcer symptomatology; three had had previous gastro-enterostomy, two had had suture of perforated ulcer, one had had gastric resection, and one had had gastro-enterostomy followed later by gastric resection. However, in about one-quarter of the group who proved to have hemorrhagic ulcer, the history was brief, nondescript and clinically inconclusive. As a rule, these were the patients with acute superficial ulcers. The

TABLE I.—*Data From 50 Consecutive Cases of Operation for Acute Massive Gastroduodenal Bleeding*

	Maximum	Minimum	Average
Age of patient.....	80 yrs.	22 yrs.	54 yrs.
Duration of symptoms....	40 yrs.	5 days	8 yrs.
Duration of bleeding.....	49 days	2.5 hrs.	4.7 days

average interval between admission and operation for the group as a whole was 12 hours, but in some instances operation was begun within two hours. The delay was usually occasioned by the procurement and processing of an adequate amount of blood for transfusion. It is true, however, that five patients had been treated for periods of seven to 17 days on a medical regimen in hospitals, and surgical aid was requested only after the internists became convinced the patients were failing.

Since the average age of the group was 54 years and some patients were quite elderly, various other unrelated diseases were often present. Four patients had hypertensive cardiovascular disease, and three others had arteriosclerotic heart disease with evidence of coronary insufficiency. Advanced cavitational pulmonary tuberculosis was present in two patients, three had pulmonary emphysema and two chronic bronchiectasis. Benign prostatic hypertrophy was present in two, urethral stricture in two, and in four there was evidence of chronic alcoholism.

For making a working diagnosis of bleeding peptic ulcer, we have relied chiefly on physical examination and history, blood studies and a process of exclusion. If portal hypertension and primary blood disease with bleeding tendency are excluded, the chances are better than nine to one in our experience that massive gastroduodenal bleeding is due to an ulcerating lesion of the stomach or duodenum. We have recntly been performing esophagoscopy

at the start of anesthesia in doubtful cases,[3] but we have not used radiologic methods of diagnosis to any great extent. In the exceptional case, roentgen ray study may be of value, but these patients vomit frequently and the stomach is often filled with clot. In a significant proportion of the cases also, the ulcers are shallow and presumably acute. These circumstances preclude finesse in radiologic diagnosis, although we do not mean to imply that such aid should never be sought in the acutely bleeding case. We have found that epigastric tenderness is usually present if searched for carefully and this sign is quite helpful in making the diagnosis.

As seen in Table II, we operated upon one patient with esophageal varices, and in two instances, a convincing explanation for the bleeding was not found at operation. On the other hand, subtotal gastric resection was performed for massively bleeding gastric carcinoma in one case, and for hemorrhagic lymphosarcoma in another. Recovery was uneventful in these five cases of bleeding

TABLE II.—*Diagnoses at Operation in 50 Consecutive Cases of Acute Massive Gastroduodenal Bleeding*

Duodenal ulcer, acute	6
Duodenal ulcer, chronic	19
Gastric ulcer, acute	5
Gastric ulcer, chronic	11
Gastric and duodenal ulcers, chronic	1
Gastrojejunal ulcer, acute	1
Gastrojejunal ulcer, chronic	2
Gastric carcinoma	1
Gastric lymphosarcoma	1
Esophageal varices	1
Uncertain	2
Total	50

from other causes, though further postoperative bleeding occurred in the patient with varices. In our opinion, unless a positive diagnosis can be made of bleeding varices or of abnormal bleeding tendency, exploratory laparotomy is in order. If active surgical therapy is withheld in cases of acute massive gastroduodenal hemorrhage, the physician assumes a grave responsibility and he should do so only for very good reasons.

When examination of the upper gastro-intestinal tract at laparotomy discloses no cause for the bleeding, the surgeon is faced with an exigent problem in surgical judgment. Our practice in this situation is to examine the stomach, duodenum, small intestine, esophageal hiatus, pancreas, liver, gallbladder, spleen and portal tributaries carefully, and if no other explanation for the bleeding is found, we proceed with subtotal gastric resection. Fatal bleeding may occur from single or multiple superficial ulcers of the stomach, or less commonly, of the duodenum, which cannot be felt, and visible serosal changes may be lacking. In about 20 per cent of the cases in this series, shallow bleeding ulcers which could not be detected at exploration were found in the removed specimen.

When we use the term "definitive treatment" in relation to this group of cases, we have a double meaning in mind. Not only is life-endangering bleeding arrested, but the peptic ulcer tendency is treated by an operation which offers the patient the best prophylaxis against recurrence of ulcer. In most instances, the same type of subtotal gastrectomy is performed which yields about a 90 per cent satisfactory five-year relief when performed for any of the other surgical complications of peptic ulcer. Follow-up studies on the present series of cases show an early promise of results equally as good as when the operation is done less urgently for obstruction, penetration or intractability of pain.

The standard gastric resection used in these cases consists of removal of 80 per cent of the stomach, as shown by actual measurements. The resection includes the ulcer when gastric in location, and it includes about two-thirds of the duodenal ulcers. All the pyloric mucosa is removed, the right and left gastro-epiploic arteries are ligated, as well as the right and left gastric arteries

TABLE III.—*Type of Operation Performed in 50 Consecutive Cases of Operation for Acute Massive Gastroduodenal Bleeding*

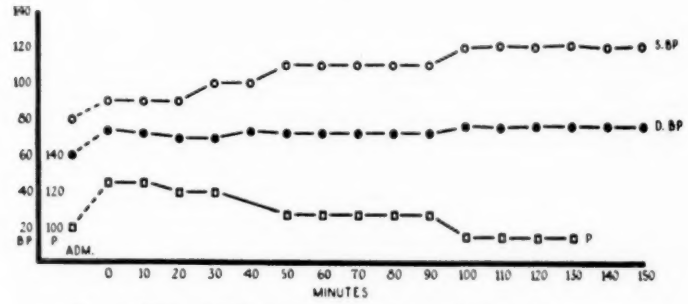
Operation	Number	Deaths
Standard (80%) gastric resection	40	2
Gastric resection with resection of gastrojejunostomy	1	0
Gastric resection with resection of jejunum and transverse colon	1	1
Gastric resection and excision of pyloric mucosa	4	0
Total gastrectomy	1	0
Total gastrectomy after gastric resection	1	0
Exploratory laparotomy, only	2	0
Total	50	3

and the recurrent and supraduodenal branches of the pancreaticoduodenal artery. In no instance, has the gastroduodenal artery itself been ligated in its supra-pyloric aspects. A Hofmeister, short loop antecolic anastomosis has invariably been used, and in almost every case, a left subcostal incision which crosses the midline has been employed. As shown in Table III, standard gastric resection was performed in 40 of the 50 cases. Prior surgical operation on the stomach necessitated modifications in several cases, and in one instance, the gastric ulcer was high on the lesser curvature and surrounded by so much inflammatory reaction that total gastrectomy was deemed advisable. Special interest attaches to the penetrating posterior wall duodenal ulcer with large pancreatic crater and much edema and induration of the surrounding tissues. In four such lesions, the operation described by Allen and Benedict was used to advantage, the pyloric mucosa being excised after isolation and devascularization of the pylorus and proximal duodenal margin.[4]

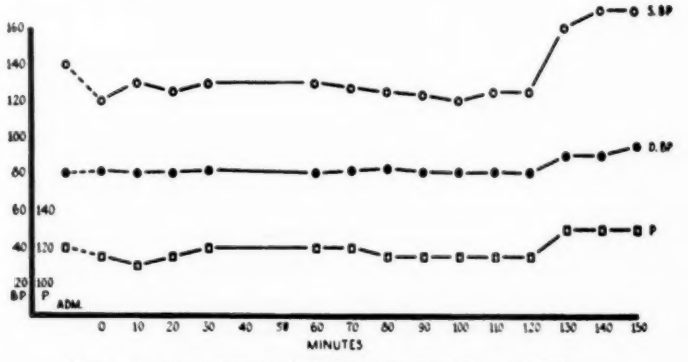
In this series, a frequent finding at operation has been distention of the stomach by a large collection of jelly-like clots. It is very helpful in this situation to free and immediately transect the pyloric antrum. The stomach is then

completely evacuated through its distal end without contamination of the field, care being used not to express blood into the esophagus. The operation is greatly facilitated by this maneuver. Ether-oxygen mixture given through an endotracheal tube has been used routinely for anesthesia. The anesthesia aspects of this problem are being analyzed in a separate communication.[5] However, it may be stated here that in these 50 cases the patient's condition

FIG. 1



R.R. - GASTRIC RESECTION FOR BLEEDING DUODENAL ULCER.
2500 cc BLOOD GIVEN DURING OPERATION



C.D - AGE 80 - GASTRIC RESECTION FOR BLEEDING GASTRIC
ULCER. 2500 cc BLOOD GIVEN DURING OPERATION

FIG. 2

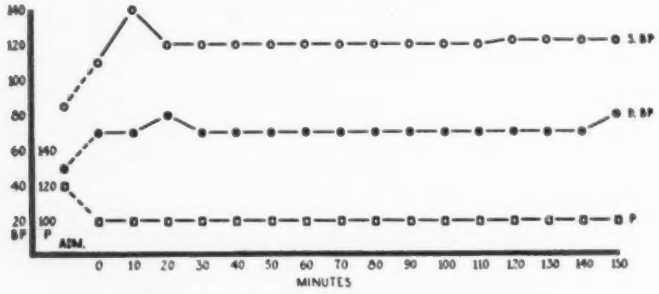
FIGS. 1 and 2.—Systolic blood pressure, diastolic blood pressure and pulse reaction during gastric resection for massively bleeding peptic ulcer. Ether anesthesia.

was almost always better at the end of operation than at the beginning. Figures 1, 2 and 3 illustrate this point.

The postoperative complications in this series of cases (exclusive of the three fatal cases summarized below) involved chiefly the cardio-respiratory system and the laparotomy wound. In six patients, there was poetoperative atelectasis, in one, bronchopneumonia, and in another, pulmonary infarction.

One patient developed cardiac decompensation and two, wound infection. In three patients there was wound separation of varying degree, and in three, there was some drainage of blood from the nasogastric tube for two or three

FIG. 3



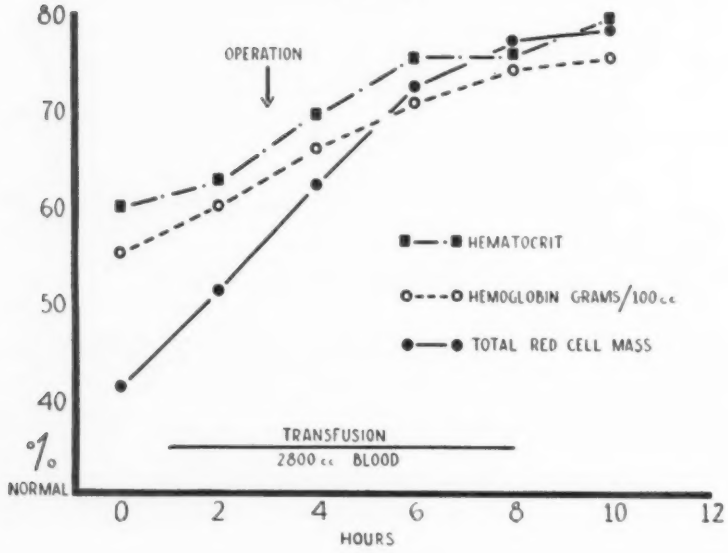


FIG. 4

FIG. 3.—Systolic blood pressure, diastolic blood pressure and pulse reaction during gastric resection for massively bleeding gastric ulcer. Ether anesthesia.

FIG. 4.—Postoperative values for circulating red cell mass, hematocrit and hemoglobin conc. in massive hemorrhage from peptic ulcer. Therapy by operation and blood replacement—values in 45 cases shown.

days after operation. There were two mild and one severe hemolytic transfusion reactions. Postoperative gastric retention was not noted, but in two patients there were mild symptoms of the so-called "dumping syndrome."

Postoperative anuria was not encountered in this series of cases. The three fatal cases are briefly abstracted.

M. B., a 75-year-old man, was admitted to the hospital with a 4-day history of melena, weakness, disorientation and convulsions. The gastric contents were bloody and the total circulating red cell mass was 18 per cent of normal. Gastric resection was performed 5 hours after admission, during which procedure 2500 cc. of blood were administered. Because of urinary retention and strictured urethra, suprapubic cystostomy was also performed. Evidence of intestinal obstruction and bronchopneumonia supervened and death occurred 11 days after operation. Autopsy was not performed.

A. L., a 60-year-old woman with a long history of peptic ulcer, was admitted to the hospital after 9 days of continued hematemesis and melena. The total circulating red cell mass was 23 per cent of normal. Subtotal gastrectomy was performed within 24 hours of admission, 4580 cc. of blood being given to her. The patient died on the fourth day after operation with signs of peritonitis, bronchopneumonia and cardiac decompensation. Autopsy was not performed.

F. B., a 51-year-old man, was brought to the hospital with a 4-hour history of massive hematemesis. Similar hemorrhages had occurred one, 12 and 28 years previously. Gastro-enterostomy had been performed 30 years before. The total circulating red cell mass on admission was 37 per cent of normal. The patient was operated upon within 12 hours, 3250 cc. of blood being given. Subtotal gastrectomy with resection of jejunum and transverse colon and cecostomy was carried out for penetrating marginal ulcer. The patient developed bronchopneumonia, wound infection and dehiscence, subphrenic abscess and gradually failed, death occurring 45 days after operation. Autopsy confirmed the clinical diagnoses and showed also multiple hepatic abscesses.

It is probably not necessary to point out that the successful surgical treatment of acute massive hemorrhage from peptic ulcer depends on the proper use of blood transfusion. Yet, in our opinion, surgeons and internists handling these cases have paid too little attention to hemoglobin-lack in the past. The simple facts that bleeding patients die of anoxia, that the longer anoxia goes uncorrected the greater the danger, and that in the anoxia of hemorrhage there is no substitute for hemoglobin, must form the conceptual basis for the management of the disease. If one considers two other facts, namely, that it is impossible to say with assurance whether bleeding has ceased and whether it will recur, and secondly, that bleeding from peptic ulcer can be surgically controlled, then the program of management which we advocate would seem to be a reasonable one.

Studies of the physio-pathology of hemorrhagic shock, stimulated by the problems of warfare, have produced new evidence on which to base restorative therapy in the condition. Acute losses of 50 per cent or even more of the total circulating red cell mass may not be immediately fatal in the previously healthy individual. In such patients, the only critical deviation from the normal prior to the onset of progressive organic deterioration is hemoglobin-lack. Large amounts of blood are urgently needed, much larger quantities than was formerly realized. In Table IV are shown pertinent data from the present series of cases. The average amount of blood given these patients in connec-

tion with operation was 3900 cc., and yet the red cell count rose from 2.6 mill/cmm. only to 3.7 mill/cmm., and the total circulating red cell mass increased from 43 per cent of normal only to 74 per cent. Since postoperative hemorrhage was not a problem in these patients, and since blood loss at operation averaged only 400 cc., it is clear that three liters of blood did not meet the replacement needs of these patients. Four or five liters would have been a more suitable quantity. Postoperative transfusion therapy was employed too little in this series of cases. Actually, 44 of the 50 patients received no blood at all postoperatively, chiefly because there was no further evidence of bleeding and convalescence proceeded satisfactorily.

It is important to realize that the data presented in Table IV are average data for the group. Evaluation of the hemorrhagic state of the individual patient is impossible without direct determination of total circulating red cell mass.[6] The reliability and practicability of the T-1824 dye technic for this purpose, as developed by Gregersen, has been amply substantiated.[7] A common

TABLE IV.—*Laboratory Data in 50 Consecutive Cases Operated Upon for Acute Massive Gastroduodenal Bleeding. Average Values Shown*

	Preoperative	At Discharge
Red cell count.....	2.6 mill./cmm.	3.7 mill./cmm.
Circ. red cell mass.....	43% normal	74% normal
Plasma protein.....	5.7 Gm./100 cc.	6.4 Gm./100 cc.

mistake in the current discussions of this subject is failure to report values for total circulating red cell mass. As a result, unwarranted and fallacious comparisons are made of various methods of treatment. During the earlier stages of severe hemorrhage, vasoconstrictive shunts and delay in hemodilution may suffice to maintain systolic blood pressure and red cell count within relatively normal ranges while total red cell mass is falling. Later, the characteristic rise in plasma volume and over-dilution of the blood may be associated with a rapid drop in red cell count and simulate further hemorrhage, whereas total circulating red cell mass may actually be increasing somewhat. The early disparity between concentration and circulating quantity of red cells is brought out in Figure 4, which is a composite presentation of data from 45 cases. The inadequacy of the amounts of blood given, which averaged 2800 cc., is also apparent.

In conclusion, our experience as analyzed in this report leads us to the conviction that early gastric resection offers the best results in the treatment of acute massive hemorrhage from peptic ulcer, provided proper surgical and transfusion facilities are at hand. The method is definitive in that anemia can be corrected, bleeding can be arrested, and the tendency to form new peptic ulcers can be controlled.

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BLEEDING PEPTIC ULCER

FAVORABLE RESULTS BY CONSERVATIVE TREATMENT*

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THE EXISTING CONTROVERSY regarding therapy in the actively bleeding peptic ulcer has largely resolved itself into a question of medicine versus surgery. This is unfortunate, inasmuch as the overall treatment of peptic ulcer is overwhelmingly in the province of the medical man, surgery correctly being employed only for the complications. Admittedly, hemorrhage is a complication of the ulcer, but it has not been demonstrated that surgical treatment is the method of choice. Consequently, the division of judgment, thought, and action has evoked "sides" and the surgical and medical literature invariably contains reports in which each side endeavors to bolster the merits of its form of therapy. There is great variation in the reported mortality figures.[4, 5, 8, 9, 17, 19, 22, 29] Those surgeons who have vigorously employed early surgery have been tempted to do so because of existent high medical mortality rates in their institutions, and the introduction of early surgery has lowered the overall mortality in these instances.[24] There can be no criticism or blame directed against surgery under these circumstances. For instance, Heuer[16] lowered the overall death rate from 13 per cent to 8 per cent by early surgery in some cases. Wangensteen,[27] Allen,[1, 2] Gordon-Taylor,[14] and Holman[18] have shifted to surgery in some cases because they have lowered the death rate in their respective hospitals. Finsterer[13] and Stewart[25] remain the only two, however, who do not carefully select their cases for surgery. They favor immediate operation when gastro-intestinal bleeding is reasonably suspected to be due to ulcer and employ Finsterer's "golden rule" of performing the operation during the first 48 hours of the hemorrhage. Finsterer's point, that the surgical mortality is low when the operation is done early (5.1 per cent) and high when performed after 48 hours (30 per cent), has been verified by others, and must be accepted as fact. Heuer states that the surgical mortality can be extremely high if performed later than 48 hours (70 per cent) and intimates that the rate increases with the passage of hours. Gordon-Taylor, Amendola,[3] Hinton,[17] and Wangensteen are only a few of many others who

* Read before the American Surgical Association, Colorado Springs, Colo., April 20, 1950. Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

have participated in establishing this point. Finsterer attacks the medical therapists with a tone of bitterness, yet he does not state their mortality rates. Perhaps the trouble stems from this fact. Meulengracht[21] has repeatedly reported his mortality rate with medical therapy familiarly known as the "Meulengracht regimen," and the figure has hovered in the neighborhood of 1.5–2.5 per cent, the world's best record, yet it has not been accepted with enthusiasm by medical men or surgeons, whose mortality figures were greatly in excess of Meulengracht's. This inconsistency provides a part of the reason for this communication. Recently, several more favorable reports of conservative therapy have been reviewed with figures as low as 4.0 per cent,[20] 3.6 per cent,[28] and 2.0 per cent.[12] These studies have been made on large enough numbers of cases with long enough follow-up periods to be significant.

It is impractical in a communication of this type to include a historical review of the literature. Lewison[20] in a recent report has admirably and completely reviewed the published data. Amendola has reported a survey of the recent surgical implications of the condition.

It should be borne in mind that the fundamental objectives of bleeding ulcer therapy are: (1) to save life; (2) to prevent recurrence of bleeding; and, (3) to control the ulcer and its possible complications in the future. It is our opinion that the saving of life is the most important objective when the patient is actively bleeding, and our efforts are directed accordingly. We feel that objectives (2) and (3) should be realized along with objective (1) if it is feasible, regardless of whether the therapy is medical or surgical, but if not believed to be feasible, we cast aside objectives (2) and (3) and plan a definite attack to solve them in the future, but early enough to be regarded as preventive as far as the next bleeding episode is concerned.

The deliberate conservative approach to the problem began at Kennedy Hospital in the summer of 1946. Since that time we have treated 171 cases, 150 of which are proved to be peptic ulcers and the other 21 cases of which are designated as probable ulcers. It is recognized that a number of the so-called "probables" are true ulcers, but have not been included because of uncertainty. There have been no deaths in that group, so that mortality figures can only be altered favorably by their inclusion.

At the present time, gastric acidity in volume as well as degree is believed to be the major factor in the maintenance of the ulcer and bears a direct relation to the complication of the ulcers. The efficacy of medical and surgical therapy is believed to be directly proportional to their ability to decrease both volume and degree of gastric acidity. It is logical, therefore, to assume that in the case of the bleeding ulcer, the high acid content of the gastric juice can be responsible for the failure of the bleeding vessel to clot effectively and for re-digestion of clot when once formed.

The patient with gastro-intestinal bleeding is, therefore, studied promptly. The first decision arrives at some conclusion about the source of the bleeding,

i.e., to establish whether the source is in the lower gastro-intestinal tract or upper. In the majority of instances this can simply be accomplished from the history, physical examination, and rectal examination which affords a direct observation of the blood content in the feces as well as the actual state of the rectal mucosa. The vast majority of cases with upper gastro-intestinal tract bleeding are due to ulcer, preponderantly duodenal and less frequently gastric in location. Confusing this issue we have observed esophageal varices, gastric polyps, neoplasms, leiomyoma of the small bowel, and Meckel's diverticulum, etc.—conditions which can produce the exact picture of the bleeding peptic ulcer. While one is studying the patient clinically and from the laboratory standpoint, measures have been put into effect to begin the transfusion of blood, which is often accomplished minutes after the patient has entered the ward. The blood is allowed to flow by the drip method unless the vital signs are markedly depressed, in which instance a more rapid rate is assumed until the vital signs reflect a safer state.

The medical therapy upon entrance includes the following:

1. Absolute bed rest and quiet.

2. Sedation with drugs other than morphine, for the latter produces gastric hypersecretion and hypermotility, and occasionally undesired nausea and vomiting. Barbiturates appear to serve this function best.

3. Our regimen is similar to the Meulengracht regimen. It changes, however, to two hourly feeding day and night, so that neutralization of the acidity by food can be continuously exerted. The food chosen is mechanically soft to avoid trauma, and is high in protein, for it is that food component alone which is antacid. The simpler foods are, however, usually attempted first. Patient's choice of food is often allowed, because we have found that the dictates of the patient's appetite will occasionally prevent nausea or vomiting.

4. Neutralizing powders[23] in milk for night feeding, calcium carbonate (0.9 Gm.), magnesium oxide (0.1 Gm.), and tincture of belladonna 1.5 cc. every six hours or atropine Gr. 1/75 if vomiting is present.

5. Psychotherapy. Assurance and reassurance allay apprehension if possible. This is extremely important.

6. Observe patient with the idea that a responsible decision must be made about the employment of surgery during the first 48 hours of bleeding.

7. Awareness in the minds of all observers that operation after 48 hours is attended with high mortality rates surgically and that shortly after the 48-hour period the surgical prognosis is worse (70 per cent Heuer, 50 per cent Gordon-Taylor, 30 per cent Finsterer) than the medical, and that if the state of the patient is poor, operation should not be done because of these facts.

8. Abstinence from tobacco is enforced.

Associated pyloric obstruction is a matter of great concern because it increases the danger of the condition. If patient is vomiting on admission, food is withheld for a period of several hours; then simple foods in small amounts

are attempted. In the meantime, sedation, assurance, and atropine exert their influence, and food can often be tolerated. Once tolerated, the diet is slowly increased in amount and frequency until the food phase of the regimen is established. If vomiting recurs, the same omission and early retrial of food consumption by mouth is resumed. In the operated group four patients showed signs of obstruction. All but one responded to the medical therapy. It may be unnecessary to state that some of the vomiting is the result of spasm rather

TABLE I.—*Apparent Severity Distribution.*

Lowest R.B.C. in Millions	Number
1.0–1.5	7
1.6–1.9	9
2.0–2.5	29
2.6–2.9	23
3.0–3.5	41
3.6–4.0	17
4.1–4.5	9
4.5+	15
Total	150

than true organic obstruction and, consequently, psychotherapy, atropine sedation, and rest could be expected to produce a release of the obstruction. Repeated hematemesis in spite of treatment will eventually establish an indication for surgery. It was one of the reasons why Case S. B. was subjected to early operation.

A few comparative pertinent facts require brief comment. Forty-five cases (30 per cent) of the series experienced depression of the R. B. C. below

TABLE II.—*Age Distribution.*

Age	Number
10–19	1
20–29	50
30–39	46
40–49	13
50–59	29
60–69	11
Total	150

2,500,000 (Table I). These would be regarded as "massive," "exsanguinating," or "critical" by many observers. Sixty-eight cases (45.3 per cent) endured depression of the R. B. C. below 3,000,000. Our experience does not justify this type of classification. Several of the bleeders below 2,000,000 recovered promptly with the use of 1000 to 2000 cc. of transfused blood. Also the rate of bleeding did not necessarily stipulate the seriousness of the episode. Large amounts of transfused blood were continued with success, and in many instances as much as 3000 cc. were transfused before hemorrhage finally slowed. We regard transfusion as a means to maintain anti-shock equilibrium

while the various medical neutralizers, etc., provide cessation of the clot digesting mechanism.

The grouping according to age (Table II) is not significant in this series as far as incidence of the condition is concerned. Our clientele include veterans of the Spanish-American War and the two World Wars and, consequently, there is paucity in certain age group material. Ninety-seven patients (64.7 per cent) were younger than 40 years while 53 patients (35.3 per cent) were older than 40 years. The dividing line of seriousness dictated by age has been established at 40, 45, or 50 by various reporters. Our older age group, like those reported by others, contains the lesser number of cases. While our 40 cases above 50 years of age include 11 cases in the sixties, we have not treated any in the seventies or eighties. All observers agree that bleeding peptic ulcer in the aged is attended with much higher mortality rate than in the young. This is not a unique fact in bleeding ulcer alone. The same can be said about appendicitis, gallbladder diseases, prostatic surgical conditions, and hernia, for instance. Nevertheless, it strongly suggests that the control of the hemorrhage in those 45 years of age and above should be gained with dispatch, even if, to accomplish the early cessation, operation must be performed in the stage of active bleeding. Our two deaths, one with medical therapy alone, and the other with combined medical and surgical therapy, were in the older age group.

The Hampton[15] technic for obtaining roentgenograms of the acute bleeder was employed in many of the cases. In the operated group it was used in eight of the 24 cases. All cases included in this report were submitted to roentgen ray examination, and proof of the existence of ulcer obtained. Niche formation or deformity of the bulb were necessary for roentgenographic verification. Spasm, "duodenitis," slow passage of barium, and irritability of stomach or duodenum were not allotted to ulcer, unless a niche or deformity was also present.

The overall mortality for this group is 1.3 per cent (two deaths). For comparative mortality figures as defined by age, the mortality rate above age 50 is 5 per cent; above age 40 is 3.8 per cent, while under age 50 it is 0 per cent.

Operations during period of active bleeding. The two cases subjected to early emergent operation require brief comment. The first was a white man in his early fifties who had bled profusely for 12 hours prior to admission. Blood transfusion was continuously employed over a period of six hours. During this time there was repeated hematemesis and the passage of bright red blood per rectum. Blood pressure remained low, pulse rate high, and the patient could not be calmed. Exploration revealed the fact that there was marked gastritis which later was learned to be due to alcohol. Gastrostomy was employed for search of the bleeding point. Recovery without incident ensued. This case is not included in the number of cases studied, but is mentioned because the operation was performed with a working diagnosis of bleeding

ulcer. The second was a 48-year-old clergyman, a known duodenal ulcer case, who has seen numerous cases of bleeding ulcer patients in his hospital work. Hematemesis and fresh bloody stools were intermittent for a period of 24 hours. He was placed upon the regimen. Four thousand cc. of Rh negative blood were transfused, but at the end of another 12 hours hematemesis and melena continued, shock could not be counteracted by these methods, and gastric resection was followed by dramatic recovery. Obviously this vomiting patient could not receive the neutralizing benefits of food or alkalis. It is our considered opinion, however, that the main factor for failure of medical therapy in this case was the inability of the patient to accept reassurance concerning his recovery. He remained tense, apprehensive, frightened, mentally overactive, and suspicious about the employment of surgery, which he accepted with decided reluctance. His efforts to avoid surgery may have precipitated the need for surgery.

Consequently, one case received gastric resection during the stage of active bleeding.

Deaths.—1. A 58-year-old Negro died on the sixth day after admission; diet and replacement therapy had failed to prevent bleeding. On the afternoon of his death plans were hastily formulated for a desperate surgical attempt to arrest hemorrhage, but the patient died suddenly during these preparations. This case was undoubtedly lost because of our procrastination and insistence upon a continuation of medical therapy past the point of time when safe recovery could have been expected surgically. Roentgen rays revealed an indeterminate antral lesion. Postmortem examination was denied. All studies, however, strongly suggest the possibility of peptic ulcer as the likely diagnosis.

2. A 55-year-old carnival performer had experienced numerous bouts of bleeding and obstruction during the 30 years he lived with his ulcer. A surgeon in the 1920s had convinced the patient that surgery could not correct his condition, so naturally he resisted the later advices about surgery until his condition became extremely dangerous. He was cachectic, was bleeding profusely, and gastric washings collected asparagus tips that he had eaten three weeks before the lavage, along with blood. After several weeks hovering between life and death he finally recovered from the active bleeding episode and immediately left the hospital against advice. One month later he returned with slight bleeding but marked obstruction. This was approximately 2 months following the successful arrest of the terrifying hemorrhage of the previous admission. This time he accepted operation reluctantly. He had a huge fibrosed stomach with a quarter size gastric ulcer on the posterior wall of the stomach which had perforated into the pancreas. The fibrosis extended above the cardia. A difficult gastric resection was performed. No other surgical procedure except vagotomy could have been accomplished with ease, and vagotomy would not have been logical in this obstructed stomach. He pulled the Levine tube during the first 24 hours. We were unable to re-insert it. He did fairly well for the first 8 days and then died of peritonitis. Suture lines were intact. A jejunostomy was attempted in desperation two days before death.

The second death did not occur because of surgery applied in the stage of active bleeding, but followed 2 months later and was due to technical error. Total gastrectomy would have been a safer operation. Drainage of the pancreatic perforated site might have prevented the peritonitis. Inasmuch as the problem on the first admission was that of hemorrhage, we enter his death

as one against the conservative method, to assure the fact that we have not allowed bias to alter our figures.

In order to clarify another point about hospital deaths, the only death which may have been suspected due to possible mistaken identification was one of esophageal varix hemorrhage, diagnosed clinically and proved at post-mortem examination. There were no deaths in the leiomyoma, Meckel's diverticulum, hiatal hernia group, etc., other than this one. We are certain therefore that no hidden peptic ulcer hemorrhage death is present in deaths from bleeding conditions other than ulcer.

Obviously then, the handling of our patients has been carried out with a co-operative spirit on the part of physicians as well as surgeons. The cases are admitted to the medical wards. Surgeons are invited to partake in judgment of action. The 48-hour deadline has been established and warns the physician not to pass it without decision. At the same time, surgeons are prompted to state the need of operation before the deadline. In most instances there has been unanimity of thought. Five cases were selected for possible surgery by our medical confreres, who, because there was not surgical agreement, were not operated upon in the active state of bleeding; all survived. The onus of recovery, therefore, weighs heavily upon each responsible physician or surgeon. When a physician decides to treat conservatively past the 48-hour period, recovery by that method is demanded by the surgical department and, consequently, the finest medical therapy possible follows. The decision is made upon well-known facts about the condition and the inability to replace the loss of blood without serious reverses. Early operation is seriously considered when the age is 45 or over, when the vital signs indicate that serious hemorrhage is occurring in spite of replacement, when obstruction is suspected, when diabetes is present, when the patient has been apprehensive and alarmed to the degree that calming reassurance cannot be established during the early phase of active bleeding, when the ulcer is known to be gastric, when previous bleeding episodes have been massive enough so that the patient was considered to be fortunate in having survived one or more of the attacks. We maintain that the now increasingly condemned term "surgical judgment" should and must be employed, as it has been found to be worthy, and adds to safety of patient. The attempts to establish the state of blood loss by studies of the blood and the effect of the replacement upon the blood picture[11] are not believed to be accurately prognostic. The degree of dehydration, lag in blood picture behind the actual loss, and physiologic attempts of the body to correct the defect by tissue fluid, vasoconstriction and other phenomena may lead to unnecessary dangerous operation at times. It is tempting to utilize some measured objective method instead of clinical judgment, but to date no such method can accurately predict the true expected course. Nevertheless, the laboratory findings are extremely helpful in formulation of opinion. Blood urea nitrogen observations determine severe degrees of bleeding when elevated. Some of our cases with elevated blood urea nitrogen have eventually recovered by medical ther-

apy. This test alone has not been the accurate prognosticator as indicated by some.

Brief comment upon the use of blood transfusion is in order. Without blood replacement, the massive bleeder cannot safely be treated either medically or surgically. Transfusion drip is continued almost constantly during the

TABLE III.

Case	Site	Age	Obstruction	cc. Blood Preop.	No. Days Cessation of Bleeding to Operation	Operative Procedure	Ulcer Removed	Complication	cc. Blood Postop.	Result
C.B.	Duodenal	27	Yes	None	100	Resection	Yes	Hematemesis Melena	6,000	Recovered
S.B.	Duodenal	48	No	4,000	0	Resection	Yes	None	None	Recovered
W.B.	Duodenal	30	No	16,500	15	Resection and vagotomy	Yes	None	None	Recovered
R.J.	Duodenal	52	No	4,500	20	Resection	Yes	None	1,000	Recovered
P.J.	Duodenal	56	No	1,500	10	Resection	Yes	None	1,500	Recovered
H.M.	Duodenal	41	No	4,000	52	Resection	Yes	None	1,000	Recovered
L.S.	Duodenal	25	No	6,500	15	Resection and vagotomy	Yes	None	500	Recovered
B.S.	Duodenal	61	No	3,000	28	Resection	No	Auricular fibrillation	1,000	Recovered
H.S.	Duodenal	51	No	3,500	9	Resection	No	None	1,500	Recovered
J.S.	Duodenal	24	No	1,500	51	Resection and vagotomy	No	None	500	Recovered
C.U.	Anastomotic	25	No	1,500	16	Vagotomy	No	None	None	Recovered
D.W.	Duodenal	21	No	3,500	14	Resection and vagotomy	Yes	None	500	Recovered
B.W.	Duodenal	54	No	3,000	24	Resection	Yes	None	None	Recovered
J.DeP.	Duodenal	23	No	None	21	Resection and vagotomy	Yes	None	None	Recovered
C.Y.	Duodenal	43	Yes	None	45	Resection and vagotomy	Yes	None	None	Recovered
L.S.	Gastric	55	Yes	4,500	27	Resection and splenectomy	Yes	Peritonitis	1,000	Died
J.C.	Duodenal	38	No	5,000	1	(?) Resection	Yes	Intestinal obstruction	1,000	Recovered
P.P.	Duodenal	31	No	3,500	18	Resection	No	Ureteral calculus	500	Recovered
F.C.	Duodenal	23	No	None	23	Resection and vagotomy	Yes	None	500	Recovered
M.W.	Duodenal	53	No	3,000	22	Resection	Yes	None	1,000	Recovered
W.S.	Gastric	58	No	4,000	53	Resection	Yes	Dehiscence	500	Recovered
H.C.	Duodenal	52	Yes	2,500	8	Resection	Yes	None	500	Recovered
F.J.	Duodenal	35	No	None	127	Resection	No	None	None	Recovered
C.B.	Duodenal	45	No	2,500	18	Resection and vagotomy	Yes	None	500	Recovered

early stages. For severe hemorrhage we have found that patients will require as much as 16,500 cc. and we would give more when necessary. Many require 2500–4000 cc. The pulse, blood pressure, color, urinary output, degree of sweating, restlessness, mental alertness are important simple vital signs that can be easily and quickly observed and at frequent intervals. We do not rely on pulse and blood pressure observations alone. It is preferable that the blood pressure remain at a level slightly below normal, so that clotting may more readily occur, but under no circumstances must shock levels be permitted to allow irreversible renal, hepatic, and vascular damage. The rate and fre-

quency of transfusion will vary, therefore, according to the above criteria. Skill is required in the judicious administration of the transfusions. One obvious point about the use of blood transfusion demands an unlimited source of available blood of the proper compatibility, regardless of type or negativity of the Rh factor. Consequently, it requires an excellent laboratory which can quickly and accurately prepare blood for this profuse administration. Also, it demands that the employees responsible for transporting the blood and labelling of the various specimens and containers be trustworthy people. Reactions should remain at a level of 5 per cent or lower, and no fatal reaction should appear in a smoothly running institution.

The final consideration for the actively bleeding case is to plan the future attack to prevent subsequent hemorrhages and to control the ulcer without other complications. Again medical and surgical co-operation must be enthusiastically smooth in order to achieve the best results. Gastric resection is recommended in the following cases in patients who have recovered from the active bleeding:

1. Repeated hemorrhages if recurrence of the hemorrhage has followed one or more serious attempts to prevent it by medical therapy and patient education.

2. All massive hemorrhages when, during the active bleeding, cessation was not easily and promptly observed.

3. When the hemorrhage proved to be from a gastric ulcer.

4. When the complications of obstruction or history of previous perforations is at hand.

5. When the patient is 50 years old or older, and circumstances following serious study of the case indicate that control of the ulcer cannot permanently be maintained by medical therapy.

6. When intractability is present after one or more adequate medical attempts.

Time for interval operation. Medical therapy continues in the hospital for a period of time averaging approximately three weeks. Operation is performed one to two months following cessation of medical therapy. We deem it important in the massive bleeders to operate before opportunity is allowed for recurrence of the hemorrhage. This period of time has proved to be successful in our experience. No case has resumed bleeding in this interval of time. Several patients refused operation and a few of them experienced recurrent bleeding. In this respect some of the patients are hospitalized throughout the entire treatment, *i.e.*, medical therapy for active bleeding and interval period awaiting and preparing for gastric resection, because the study of these cases has revealed conditions in the environment of the home or work which, to us, appeared to be psychogenic impulses that might have been responsible factors in the etiology of these ulcers. Regardless of the accuracy of this statement, it should be mentioned that in every instance successful results were obtained.

We have accepted gastric resection as the surgical procedure of choice in this condition whether the operation is performed during the state of active bleeding or during the later interval. Gastro-enterostomy, ligating and plicating procedures have not proved satisfactory. Vagotomy, combined with gastro-enterostomy, has not been employed at Kennedy for this condition. Vagotomy accompanied the gastric resection in eight cases, but only as an auxiliary procedure which would aid the lowering of the acidity. It was employed in the younger age group six times and twice in the older group. These cases were regarded as most likely to recur and every possible surgical aid was therefore employed. Time and further observation may indicate the ancillary use of vagotomy for a greater number of cases. We have observed no ill effects from vagotomy in this small group. Vagotomy alone proved highly successful in the treatment of our seriously hemorrhaging anastomotic ulcer patient. Further observation may conversely indicate that vagotomy should not be employed at the time of resection, but should be reserved as a successfully hopeful maneuver if the dreaded anastomatic ulcer should occur after high gastric resection. Incidental splenectomy was performed in the difficult fatal case because the vessels in the gastro-lienal ligament had been injured. Our lack of experience does not qualify us to comment about the efficacy of vagotomy or of vagotomy plus gastro-enterostomy in the bleeding peptic ulcer.

Operations during period after recovery of active bleeding. The indications selected for operation as cited above necessarily limit the number receiving the operation. The patients are prepared for surgery the same as the non-bleeding cases. Retrocolic gastric resection of the Hoffmeister type has been employed in all cases and has been successful except in the case of the extremely complicated problem of the carnival worker. The operation at this time is naturally more easily performed and frequently allows the removal of the ulcerated area. These two advantages increase the degree of safety for these patients. Many of the operations are done by members of the resident staff. According to Walters,[26] gastro-enterostomy is attended by a 23.8 per cent rate of recurrent hemorrhage, while the recurrence rate after gastric resection is only 3.6 per cent. We expect that a number of the medically controlled group may require surgery in the future.

Local conditions which may favorably influence mortality are suspected. One of us (R. F. B.) has worked in an area where the mortality has been higher and consequently may qualify to analyze comparative results. The following are suggested:

1. Approximately 75 per cent of our patients hail from rural districts where the emotional stresses and strains are not the same as those of the larger cities. Insecurity of economic or social position does not exist in the same degree. Fear of starvation and family support is much lessened. The emotional factor may therefore be of less intensity. The stock is more like the frontier type.

2. Our patients accept reassurance and the calming influence of the efforts

in their behalf with more certainty than the urban sufferer. This possibly could be associated with ignorance of the severity of his condition.

3. Many of our patients are conveyed to the hospital by ambulance from distances of 50 to 200 miles. Perhaps there are some patients in the same communities who are not transported to us because of severity of bleeding or who are bleeding so furiously that death occurs before plans can be made. If these patients lived close by, their admissions might alter our results unfavorably. In other words, we may be receiving only the favorable cases from these distant communities. Many, however, arrive exhausted and exsanguinated.

4. The number of cases above the age 45 is considerable. Analysis of other reported figures commonly indicates that the majority of cases occur between the ages of 30 and 50. But the number of our cases in the sixties is small and we have treated no cases in the seventies or eighties. Admittedly, this fact favors our low mortality, as well as the small number of cases subjected to emergency surgery. As our clientele then advances in age we should expect to employ emergency surgery in a greater number to maintain this low mortality. In this respect, it should be pointed out that the mortality below age 50 is zero per cent, which compares very favorably with the reported mortalities in the young group and that the overall mortality rate of 1.3 per cent is lower than most figures for the young group.

SUMMARY

1. One hundred fifty cases of bleeding peptic ulcer have been treated by combined medical and surgical therapy. Medical therapy has largely been employed during the state of active bleeding; gastric resection was performed in one case 36 hours after appearance of hemorrhage when apparent failure of medical measures to invoke cessation of the hemorrhage was observed.

2. Twenty-four gastric resections were performed after recovery from active bleeding. Eight of these 24 cases received vagotomy as an ancillary procedure.

3. The overall mortality is 1.3 per cent. One death followed the use of medical therapy alone. The second resulted from combined therapy; surgery was employed during the interval period. Mortality rate above 50 years of age is 5 per cent; under 50 years of age it is 0 per cent.

4. Factors which may contribute favorable influences in this group of cases are mentioned.

5. It is believed that the combined therapy, with vigilant enthusiasm by both internists and surgeons, evolves as a satisfactory method of treatment—at least for the type of patients presently being admitted to Kennedy Hospital.

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SECONDARY OPERATIONS FOR PEPTIC ULCER*

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ADDITIONAL EVIDENCE to support the contention held by Ivy,[1] Mayo,[2] and others that the incidence of peptic ulcer in this country is increasing, continues to appear in the current medical literature. Of those who have sufficient symptoms to require medical treatment, about 15 per cent, according to Heuer,[3] develop those complications that require surgical treatment. As demonstrated by Moore *et al.*,[4] this proportion has remained rather constant from one decade to another. Medical treatment, therefore, may be considered satisfactory for the majority of peptic ulcer patients, but when such measures fail, surgery will relieve most of the remaining. Of those patients who do require surgical therapy, about 80 to 85 per cent will be cured or improved by the first definitive procedure employed. Those that require further surgery, therefore, represent failure of both medical therapy and primary surgery. It is with this group that we are concerned here.

In a group of 260 patients followed carefully from two to ten years, Rienhoff[5] found that 11.1 per cent required secondary surgical treatment, chiefly because of jejunal ulceration. A review by Ransom[6] at the University of Michigan of 81 patients with postoperative jejunal ulcer reaffirms the findings of others that secondary operations have been necessary following every type of operation employed as a primary definitive procedure. Priestly[7] found that indications for further surgery commonly appear within five years, but that they may continue to arise for periods up to 25 years.

Over a period of 17 years, from 1932 to 1949, 113 patients on the pavilions of The New York Hospital-Cornell Medical Center have had secondary definitive operations performed for peptic ulcer. Approximately half of this group had their primary procedure done elsewhere. This series of patients is believed to be fairly representative of their category for the country as a whole as to their primary medical treatment, the types of operation first employed as definitive surgery and the sequence of complications that led to secondary procedures. To the surgeon who undertakes to treat them they constitute an unsolved problem. In an effort to improve the therapy accorded such patients, we have analyzed our experience with these 113 cases, giving particular attention to the type of ulcer, the primary procedure, the lapse of time between primary and secondary operation, the nature of the secondary operation, and the follow-up results that have thus far accrued. Four patients that presented particularly difficult problems are reviewed in detail.

* Read before the American Surgical Association, Colorado Springs, Colo., April 20, 1950.

One hundred thirteen patients on the surgical pavilions of The New York Hospital have been subjected to one or more secondary operations for peptic ulcer from 1932 through 1949, a period of 17 years. This group has been followed with unusual care so that only six have been lost to the follow-up department. One hundred, or 88.5 per cent, had duodenal ulcers, 12, or 10.6

TABLE I.—*Secondary Operations for Peptic Ulcer (New York Hospital-Cornell Medical Center 1932–1949)*

Type of Ulcer	No. of Patients	% of Total
Duodenal	100	88.5
Gastric	12	10.6
Both	1	0.9
	113	100%
Males	100	88.5
Females	13	11.5
	113	100%

per cent had a gastric ulcer, and one had both a duodenal and a gastric ulcer. The group was divided into 100 males and 13 females. Fifty-four had their primary definitive operation performed at The New York Hospital, since 1932, and the remaining 59 had their primary operation elsewhere, including 16 who were operated upon at the old New York Hospital prior to 1932.

TABLE II.—*Secondary Operations for Peptic Ulcer (New York Hospital-Cornell Medical Center 1932–1949)*

Primary Operation	No. of Patients	% of Total
Gastro-enterostomy	87	77.0
Gastric resection	17	15.0
Vagotomy	3	2.6
Miscellaneous	6	5.4
	113	100%

Plication previous to primary definitive operation: 17

Seventy-seven per cent, or 87 of the 113 patients, were subjected to gastro-enterostomy as their primary definite procedure, 17, or 15 per cent, to gastric resection, three, 2.6 per cent, had a vagotomy, and the remaining six, or 5.4 per cent, had miscellaneous primary procedures. Of the 87 treated by gastro-enterostomy first, 14 had local excision of the ulcer in addition. Seventeen of the 113 had plication done for acute free perforation of the ulcer prior to their primary definitive procedure.

The most common condition leading to a secondary operation has been a jejunal ulcer, either adjacent or near the junction of the gastric and intestinal mucosa, sometimes continuing with ulceration of the gastric mucosa. In certain instances there has been persistence or recurrence of a duodenal ulcer. All of these conditions have been associated with the following symptoms, by order

of frequency: pain, bleeding, obstruction, and perforation. Gastrojejunal colic fistula developed in 17 cases where the secondary operation had been too long delayed in the presence of these symptoms. The lapse of time between primary and secondary definitive procedure has ranged from 14 days to 36 years.

TABLE III.—*Secondary Operations for Peptic Ulcer: Interval Between First and Second Operation*

Time Interval	No. of Patients	% of Total
Under 1 year	13	11.5
1 to 5 years	41	36.3
6 to 10 years	29	25.7
11 to 15 years	15	13.3
16 to 20 year	5	4.4
Over 20 years	10	8.8
	113	100%

The two extremes in length of interval between operations are small in number. Thirteen, or 11.5 per cent, were operated on a second time within a year, and 10 or 8.8 per cent went for more than 20 years before their second operation. Perhaps the most significant fact, however, is that almost half of the group, 54 out of 113, or 47.8 per cent, had their second operation within five years of their primary procedure, whereas the balance of 59 patients went for a much longer interval, one to the extent of 36 years, before recurring symptoms required further surgery. Thus, although the likelihood of recurring symptoms diminishes after five years, the possibility of their recurrence is ever present.

TABLE IV.—*Secondary Operations for Peptic Ulcer: Distribution.*

Procedure	2nd	3rd	4th	5th	6th	Total
Gastro-enterostomy	13	4	1	..	..	18
Dismantling	12	..	..	..	..	12
Gastric resection	58	18	2	..	..	78
Vagotomy	14*	4	1	..	1	20
Miscellaneous	18	2	–	1	–	21
	115	28	4	1	1	149

* Combined with gastric resection in one instance and plication in another.

A total of 149 secondary operations were performed on the 113 patients over a period of 17 years. Twenty-eight patients were not cured by a second operation and required a third, four required a fourth, and one patient required six procedures in all, but is now a good result. Simple dismantling and restoration of the gastro-enterostomy was done in 18 instances; dismantling with excision of the portion of the jejunum containing ulceration, followed by end-to-end anastomosis and reconstruction of the gastro-enterostomy was done in 12 cases. Both these procedures have been followed by a very high incidence of recurrence, almost 90 per cent, and are to be condemned. It should be pointed out, however, that for the most part they were done in the early years of our period. Few have been done recently.

Gastric resection has become the procedure of increasing popularity, particularly in the last ten years. In our series it was used as a secondary procedure in 78 instances. Vagotomy, following its introduction by Dragstedt[8] in 1943, was used by us for jejunal or marginal ulceration in 20 instances. Miscellaneous procedures, including plication, pyloroplasty, pyloric exclusion, Bilroth I, entero-enterostomy, and gastrojejunal implant were used in 21 cases. All these, however, have been gradually discarded as of little value. The results of these secondary procedures follow.

TABLE V.—*Secondary Operations for Peptic Ulcer.*

Follow-up Results	No. of Patients	% of Total
Symptom free	66	58.4
Improved	12	10.6
Marginal ulcer demonstrated	5	4.4
Died ultimately of ulcer	3	2.7
Died postoperatively	11	9.7
Died of unrelated cause	10	8.9
Lost to follow-up	6	5.3
	113	100%

These figures indicate the gravity of the situation when patients are not relieved by a primary definitive procedure. The postoperative mortality rate from a secondary operation in this series is high, 9.7 per cent, and if we add to it those who died later because of their persisting ulcer, our complete failures total 12.4 per cent. Only 66 per cent of our series are now symptom free and it may be expected that some of these will have recurring symptoms in the future. On the other hand, those who are improved though not symptom free at the present time (10.6 per cent) may improve further, but it is more likely that this will not be the case and that their symptoms will increase as time goes on. It is doubtful if results on the six lost to follow-up would change the overall picture were present data on them available.

Persistent, periodic, and careful observation, followed by both established and new procedures when indicated, can convert some failures into good results. A case in point is J. C. (57–551) who has had a total of six operations between 1916 and 1947, but when last examined this year was greatly improved.

J.C.	M	b. 1892	NYH 57–551
1916	Duodenal ulcer	Gastro-enterostomy	
1934	Marginal ulcer	Dismantling of gastro-enterostomy and resection of jejunum	
1937	Duodenal ulcer	Pyloric exclusion	
1940	Marginal ulcer	Gastric resection	
1941	Marginal ulcer	Plication of perforation	
1947	Marginal ulcer	Transthoracic vagotomy	
1950	Follow-up: Free of pain. No roentgen ray evidence of marginal ulcer. Persistent anorexia.		

Some patients however, in spite of procedures that have proved most successful for the majority, continue to manifest an ulcer diathesis that seems to defy solution by surgery. The case of D. F. (445-434) is an example. Resection and vagotomy, both tried twice, have failed, and she continues to have evidence of a marginal ulcer. A primary gastric resection that removed two-thirds of the stomach was followed by jejunal ulceration to the extent of free perforation. This necessitated emergency plication and a subdiaphragmatic vagotomy was done at the same time. Because of the persistence of jejunal ulcers, further gastric resection was done, leaving an estimated 20 per cent residual stomach. Forty days later, because of hemorrhage from a new jejunal ulcer, a transthoracic vagotomy was done since it was felt that the first vagotomy might not have been complete despite insulin tests to the contrary. Two years later there exists roentgen ray evidence and symptoms of a jejunal ulcer.

D.F.	F	B. 1912	NYH 445-434
1-28-47	Duodenal ulcer	Gastric resection	
2-22-47	Marginal and jejunal ulcers	Plication and subdiaphragmatic vagotomy	
4- 7-47	Marginal ulcer	Further gastric resection	
5-17-47	Jejunal ulcer with hemorrhage	Transthoracic vagotomy	
3-22-50	Follow up: Symptoms and roentgen ray evidence of marginal ulcer.		

Another problem patient is J. J. (10-908) who was first operated upon in 1933 at the age of 40 for a duodenal ulcer. A gastro-enterostomy was done at that time and he remained symptom free for 15 years, but then developed a marginal ulcer. Vagotomy was performed and for six months he was relieved of pain and there was no evidence of the ulcer on roentgen ray examination. Less than a year later, however, his symptoms recurred and a gastric resection was done that removed three-fourths of the stomach. This has so far rendered him symptom free.

J.J.	M	b. 1894	NYH 10-908
1933	Duodenal ulcer	Gastro-enterostomy	
1948	Marginal ulcer	Vagotomy	
1949	Marginal ulcer	Gastric resection	
1950	Follow up eight months later: Symptom free.		

Finally, we present A. S. (378-111), a 46-year-old railroad employee who developed a duodenal ulcer with severe hemorrhage in 1946. This was treated by a gastric resection that removed slightly more than half the stomach. He was improved for several months but then was found to have a jejunal ulcer perforating into the liver. Further resection was done, leaving less than 25 per cent of the stomach. One year later he developed a marginal ulcer and a

transthoracic vagotomy was done. For the past six months he has been symptom free, but he has had similar periods of relief following his first two operations. It would not be surprising if he were to develop symptoms of a jejunal ulcer again.

A.S.	M	b. 1900	NYH 378–111
1946	Duodenal ulcer		Gastric resection
1948	Margin ulcer perforating into liver		Further gastric resection (residual stomach 25 per cent)
1949	Marginal ulcer		Transthoracic vagotomy
1950	Follow up six months later:		Symptom free

It should be emphasized again that many patients suffering from peptic ulcer recover and become completely free of symptoms on some sort of medical regimen. We strive to give every patient all the advantages of the best medical therapy before operation is recommended. It is obvious that the practical application of generally agreed rules for ulcer therapy will differ widely across the country. No doubt many patients should receive early surgical treatment, those with massive and exsanguinating hemorrhage for example, or those with debilitation from obstruction, or even those incapacitated because of pain. On the other hand, many have undergone surgery who would have recovered without operation. There have also been those for whom surgery was felt to be imperative but withheld for one reason or another, yet years later they have been found to be well. Perhaps these patients simply outlive their ulcer diathesis.

That ulcer is sometimes a psychosmatic disease is generally acknowledged, and undoubtedly certain ulcers have healed following psychotherapy. Instances of severe ulcer diathesis requiring secondary operation are not infrequently associated with a marked psychogenic factor. With this group of patients one may well ask the question, "Does operation ever give rise to a marginal ulcer, generally a more serious lesion than the average duodenal ulcer?" The answer is not evident.

Gastro-enterostomy for peptic ulcer was the procedure of choice for a long time because of its low postoperative mortality rate and the good results reported by many clinics that ranged as high as 80 to 90 per cent. William A. Cooper[9] reviewed a series of 279 gastro-enterostomies performed at The New York Hospital over a 13-year period, 1932 to 1945, and concluded that a patient treated by gastro-enterostomy had a 96.7 per cent chance of surviving the operation and a 78 per cent chance of remaining well without further treatment. This was an accurate evaluation of the operation for that time, but these results have now been surpassed by those of gastric resection, now more widely used. In the same clinic a patient is now (1946–1949) estimated to have a 97.7 per cent chance of surviving this more radical procedure and has an 87 per cent chance of remaining symptom free thereafter. This estimate is

based on our total experience with the procedure thus far. Longer follow up studies may not prove as optimistic.

Since the insistence by A. A. Berg[10] over 20 years ago that gastric resection was the best operative procedure for peptic ulcer, there has been not only a gradual acceptance that this is the procedure of choice, but also a trend to leave less and less stomach. Without going into technical detail, the accompanying diagram (Fig. 1) will illustrate the amount of stomach that we believe should be resected for either primary or marginal peptic ulcer. Indeed, it is now believed that the incidence of secondary operations will be reduced if a maximum portion of stomach is removed at the primary operation. There will

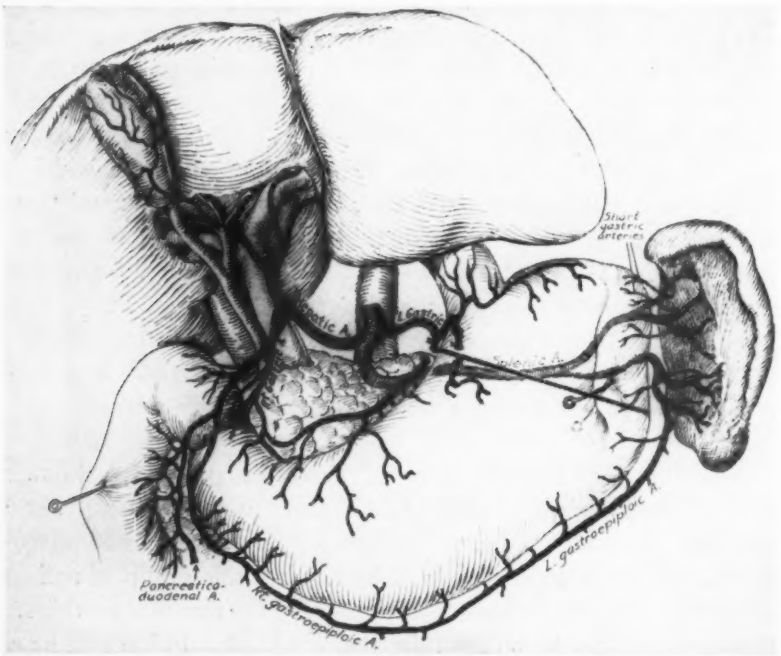

FIG. 1.—Three-quarters of the stomach should be resected together with the ulcer. Dotted line indicates level of transection.

be instances, however, when gastric resection is contraindicated for one reason or another. For these cases gastro-enterostomy, with or without vagotomy, may be accomplished with minimal risk. At The New York Hospital over a four year period from 1946 to 1949, 301 patients were treated by primary gastric resection, while 35 others were limited to gastro-enterostomy.

The place of vagotomy in the surgical treatment of marginal or jejunal ulcer remains to be established by time. On the one hand we have had brilliant results from vagotomy when all other procedures had failed, but we have also had patients who showed only temporary improvement following this procedure.

CONCLUSION

It becomes obvious from a review such as this of secondary operations for peptic ulcer that the primary operation in these cases was not adequate therapy. Secondary operations convert many primary failures into satisfactory results; in our experience this has been somewhat more than 50 per cent. When failure persists, which it has even after employment of our entire surgical armamentarium, we are faced with the fact that surgery is not the proper therapy for some patients. Here, as surgeons, we can only say that we used the best procedures we had but they were not enough. Fortunately this group is small compared to the total number of ulcer patients treated surgically, perhaps less than 5 per cent.

Although the total number of patients requiring secondary operations for ulcer is small, the mortality rate associated with secondary procedures is high. This fact should lead the surgeon to do the most desirable procedure in the first attempt at definitive therapy. However, if contraindications to this are

TABLE VI.—*Secondary Operations for Peptic Ulcer: Vagotomy Results.*

Symptom free	7
Improved	3
Marginal ulcer demonstrated	4
Inadequate follow-up	5
	19

Primary vagotomy followed by resection: 3

present at the primary operation, a compromise procedure may need be resorted to, with a view to accomplishing the ideal thoerapy at a later time when conditions are such that it can be achieved with the least possible risk to the patient.

From the studies we have made, it is evident that an adequate gastric resection, namely one that removes two-thirds to three-fourths of the stomach and that part of the duodenum containing the ulcer, is the procedure of choice. So far as resecting an ulcerated duodenum is concerned, it is suggested that if the patient is likely to run a high risk of duodenal leakage with subsequent peritonitis due to difficulty in closure, the procedure is not justified. Eastman and Cole[11] have reported a series of patients that had no ensuing complications under this policy. We have not been as fortunate. We have seen both bleeding and pain persist or recur when the ulcer is not removed, in some cases. Here, resection of the duodenal segment may be feasible in six months' time, or possibly later, if the process has not subsided sufficiently.

As to removal of three-quarters of the stomach, it would appear that this should be done more regularly, even though it is not always easy to accomplish. Conviction on the part of the surgeon that it will improve his results should encourage him to exert the extra effort needed to accomplish it. Indeed, if he studies his patient with this objective in mind, he can facilitate

the procedure by providing maximum exposure on his approach and by making sure that he has good and adequate assistance.

It is recommended, therefore, barring contraindication, that resection of three-fourths of the stomach be done for all peptic ulcers requiring surgical treatment. The probability of a marginal ulcer developing thereafter is slight, perhaps less than five per cent, but if it does occur, then vagotomy should be the next procedure. Should this fail as well, then a total or near-total gastric resection should be considered. This is the gamut of our surgical armamentarium at the present time. It constitutes an effective policy that if followed should result in a very small number of failures compared to the total number of patients treated surgically. For these few we hope that drugs such as Banthine,[12] now showing promise, will control these distressing clinical problems when they persist.

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DISCUSSION.—DR. CONSTANTINE J. MACGUIRE: I wish to discuss, very briefly, Dr. Hinton's paper. That report was based on work done mainly in the Fourth Division at Bellevue Hospital, and it interested me because at the same time we were doing similar work on another Division of the same hospital under the late Dr. McCreery.

We had begun to use subtotal gastrectomy in 1923 as a physiologic attack on peptic ulcers, but only in relatively few cases with extensive pathology.

In 1928, at the time that Dr. Hinton started his gastric clinic, we dropped gastroenterostomy entirely for intractable peptic ulcer and reserved it only for certain selected cases of pyloric obstruction. We adopted subtotal resections as the procedure of choice and confined ourselves mostly to an anterior Polya type of resection. We ran along a parallel line with Dr. Hinton, and had access to the same material from the low economic

group available at Bellevue Hospital, but we disagreed very strongly with him on one feature of his work, and that was the removal, in toto, of a duodenal ulcer. We have not found this practical. We admit it is desirable, and as Dr. Glenn just said, if you don't do it right away, you may be able to do it more successfully later.

Most of the duodenal ulcers are resectable, but there is a considerable group in the second portion of the duodenum where the crater, penetrating the pancreas with induration and callous reaction—involving the gastrohepatic omentum and the common duct—there attempts at resection will be disastrous.

Now, the decision to resect or not to resect should be made early, because exploratory dissection will land you in the lumen of the duodenum, and you have burned your bridges behind you.

Now, of course, comes the problem of "What should we do in a bleeding ulcer in this region with this pathology?" If you don't resect, you are subject to subsequent bleeding. If you do resect, you are subject to a high operative mortality.

I would like to illustrate this by the fact that in one such case I did a subtotal resection and left the ulcer in situ. Seven days later there was another very fulminating hemorrhage which autopsy showed came from the original duodenal ulcer with the crater immediately adjacent to the papilla of Vater.

In another case I attempted to resect an ulcer that I would have left alone if it hadn't been the site of a massive hemorrhage. In this case I cut the hepatic artery, with subsequent necrosis of the liver and death.

These are two not very complimentary cases, but I cite them because I think they will happen to fairly competent surgeons.

Since the first of last July, our resident at St. Vincent's Hospital has done, I think, 37 subtotal gastrectomies with only one death resulting from postoperative coronary thrombosis on the fourth postoperative day. In four cases the duodenal ulcer was not removed, as it was considered inoperable. These four cases did well postoperatively and became symptom free.

The resident surgeons in our area—and I think very much throughout the country—are doing almost all of these operations on the general service, and I think our advice to them must be carefully considered. To advise them to resect all duodenal ulcers would be very disastrous. Incidentally, our mortality at Bellevue, as gone over by Dr. Wylie recently, showed that in the last ten years it has been 2.6 per cent. In the early years it was 18 to 20 per cent.

I am very glad to have had an opportunity to discuss this paper.

Dr. Howard A. Patterson: At the Roosevelt Hospital in New York City our experience with massive gastro-duodenal bleeding has paralleled that of Dr. Stewart much more closely than that of Dr. Bowers.

For the past three years we have leaned more and more toward prompt surgery in selected cases. Of course, what we need is a crystal ball to gaze in, to find out which ones are going to stop bleeding and which are not. Not having such an apparatus, we must do the best we can.

At this hospital we have a very busy ambulance service, and most of our cases come in very promptly, and we get a lot of bad ones. I think all the cases I am going to mention fulfill Dr. Stewart's criteria of really massive gastroduodenal bleeding.

These cases are all admitted directly to the surgical service, and they are seen by the medical staff there with us, and they remain on the surgical service until a decision has been made as to whether or not an operation should be performed.

We do not hesitate to do x-ray studies, even in the bleeding phase so long as the patients are carefully handled and not kept waiting too long in the x-ray department. We send a doctor down with them.

We try to decide promptly—certainly within the first 12 or 18 hours—which ones are going to be subjected to surgery and which ones are not going to be subjected

to surgery. If we think they are not going to stop bleeding—if they behave that way—or if they stop and then start again, we operate promptly.

We have had no luck whatever, in the past, with makeshift operations. We either do the resection or nothing at all. About one massive bleeder in three is operated on at the present time.

We feel that the age of the patient has been emphasized too much, and that the age of the lesion has not been emphasized enough. We think that an old lesion in a young person will bleed about as stubbornly as a young lesion in an older person.

In the last 31 cases done according to this plan, where prompt surgery was resorted to, we have had two deaths, one of which was in a known hemophiliac of long standing. I don't know why we have never seen one before. One would think that this would be encountered occasionally. I suppose it is because the hemophiliacs don't live very long, many of them, and they are not too common, anyway. That man lived 19 days postoperatively, but in spite of all the blood we could find, he got practically no wound healing at all.

Of course, the mortality in the old days—when we used to operate only on the sort of pre-cadavers that the medical men sent to us, when they were given up—was extremely high, but I believe that today in this group of cases, with adequate blood replacement, as Dr. Stewart has emphasized, the mortality can be kept quite low.

The really tough decisions, of course, arise when you explore and find no source of hemorrhage. I am sure that most of you have seen fatal cases in which the pathologist has looked for the source of hemorrhage all day, in the autopsy room, and has never been able to demonstrate the source of hemorrhage. Those cases are the really difficult ones in deciding what to do.

Dr. Stewart's teaching is very courageous. However, it seems to me a little dangerous to teach the young man that if you don't find anything, you should take out the stomach. But this is destructive criticism, I realize.

I wish to thank Dr. Stewart and Dr. Bowers for their real contributions to this very live subject, in which I think we still have a long way to go to find the real solution.

Dr. Dallas B. Phemister: I want to report a case of ulcer of the stomach which developed after segmental resection of both vagus nerves accompanying transthoracic resection of the lower esophagus and proximal stomach for carcinoma of the esophagus five years ago in a 44-year-old man; also healing of the ulcer after gastro-enterostomy. There was no history of symptoms or radiologic evidence of ulcer before the operation. He got along well postoperatively for two and quarter years, and then he developed symptoms compatible with gastric ulcer, with postcrandial pain in the lower part of the chest which was relieved by food taking. These symptoms came periodically. Examination showed that there was gastric retention, and the overnight secretion which was collected on two occasions showed 17 clinical units of free hydrochloric acid in one specimen and 39 units in the other. Two roentgenologic studies 11 days apart revealed a 16 x 7 mm. crater on the lesser curvature 4 cm. below the gastro-esophageal anastomosis. After gastro-enterostomy which was then done, the symptoms promptly disappeared, and a roentgenogram 5 weeks later showed no sign of a crater. He has remained well for the two and a half months since operation.

No report has been found of the development of gastric ulcer following transthoracic segmental resection of a carcinoma of the lower esophagus and both vagi, and if the experience to date in this case is significant, gastro-enterostomy should be a good treatment for the complication.

Dr. Warren H. Cole: I wish to confine my remarks to massive hemorrhage in duodenal ulcer. It is rather obvious, from the discussion, that there is no agreement as to what method of treatment should be utilized, and I agree with Dr. Patterson that it may be quite some time before we arrive at the real solution.

I agree with Dr. Bowers—from the standpoint of the mortality rate reported in

literature and mortality rates reported by him—that conservative treatment would appear to be better than operative treatment. However, in spite of his very convincing presentation, I am still not quite convinced, and up to date I am operating on at least some of the patients with massive bleeding from duodenal ulcers.

My philosophy is to start blood transfusions immediately, as everybody does, and watch the blood pressure, instituting frequent feedings, and alkali. If, after six to ten hours of treatment with numerous transfusions, the blood pressure is still not approaching normal, then I send that patient to the operating room for operative therapy, under the assumption bleeding is persistent, and may not subside spontaneously.

On the other hand, if the blood pressure comes back to normal with three or four transfusions, and you put a tube down the stomach and find brown blood—no bright blood—it is rather obvious that the patient has stopped bleeding; such a patient would be continued on with medical therapy, and operated on later in an interval between attacks.

Dr. Bowers also called attention to the pinpoint ulcer, or bleeding without any gross evidence, which has been called to our attention by two or three of the essayists. That is certainly a very disappointing group of lesions to encounter, especially if you are treating them by operation. I have seen two of those, one at autopsy without operation and one at autopsy after I had operated on the patient and did not find the pinpoint lesion.

I would also like to warn that when we are operating on bleeding ulcers (and I believe that everyone agrees with this) ligation of an adjacent large artery alone is very apt to lead to failure. I did ligate the gastroduodenal artery in one of the pinpoint ulcers just mentioned, preferring not to do a gastroduodenal resection, because I could not feel an ulcer through an opening I had made in the pyloris. The bleeding persisted, and the man died. We found a pinpoint opening in the mucosa which led to a fairly large branch of the inferior pancreatico-duodenal artery. The pathologist found that, and demonstrated it very nicely.

In a recent case of hemorrhage from a large duodenal ulcer, I tried the effect of compressing the various arteries, particularly the gastroduodenal; on this particular occasion the vessel was bleeding actively, spurting into the stomach. We could see, after opening the stomach, that compressing the gastroduodenal artery exerted no control whatsoever in the bleeding, but compressing inferiorly, over the inferior pancreatico-duodenal artery, stopped the bleeding promptly. All of us know that it is a bit difficult to find the latter vessel, and I prefer to transfix the point rather than try to find the inferior pancreatico-duodenal artery.

I might add, in closing, that I have seen two patients die—and they were under 30 years of age—when treated conservatively in the presence of massive bleeding; it is largely because of this experience that I am not quite ready yet to adopt the conservative treatment for all bleeding ulcers.

Dr. James T. Priestley: I enjoyed all of these fine papers this afternoon but will confine my brief remarks to the presentation made by Dr. Glenn. In general, our experience has been similar to that which Dr. Glenn has reported. There are several points, however, on which I would like to comment.

In the first place, I think that we should always distinguish between the jejunal ulcer which develops after gastro-enterostomy and the one which occurs after gastric resection. The reasons for this are that these ulcers develop under different physiologic conditions, their indications for treatment differ, and in addition, their prognosis differs. An additional point in this regard, which was of interest to Gibson and me in a study of jejunal ulcer which we made several years ago, was that although approximately one half of all jejunal ulcers occurred within two years after the initial operation, the average length of time before the occurrence of jejunal ulcer after gastro-enterostomy was 3.7 years, whereas the average length of time before the occurrence of jejunal ulcer after gastric resection was only 1.7 years.

Regarding treatment, I might say that in our opinion, gastric resection remains the treatment of choice at the present time, for jejunal ulcer which develops after gastro-enterostomy. In selected cases this may be combined with vagotomy, but if this is done, one should remember that the patient is then subjected to any possible undesirable effects of both these procedures as well as the possible benefits. Although in former years gastric resection performed for jejunal ulcer which occurred after gastro-enterostomy was associated with a relatively high operative mortality, I believe that today gastric resection can be performed for this condition with a surgical risk quite comparable to that associated with gastric resection performed initially for duodenal ulcer. Vagotomy, often performed by the transthoracic route, appears to be the treatment of choice at the present time for the patient who develops jejunal ulcer after gastric resection, provided a resection usually considered to be adequate in amount was accomplished at the initial operation.

Late results in the treatment of jejunal ulcer which develops after gastro-enterostomy have always been more satisfactory in past years than those obtained in the treatment of jejunal ulcer which occurs after gastric resection. In the study of a significant number of patients who had jejunal ulcer which Gibson and I made, it was found that a result which was considered to be satisfactory by the patient was obtained in somewhat over 80 per cent of patients in whom gastric resection was performed for jejunal ulcer which developed after gastro-enterostomy. Less than 50 per cent of patients who had resection performed for jejunal ulcer which occurred after an initial gastric resection had a satisfactory result. All of these patients were followed a minimum of five years and some for as long as ten years.

DR. JOHN R. PAINE: I would like to refer for a moment to this problem of the treatment of the massive bleeding ulcer, and to further complicate the matter, I should like to bring up the Rh factor.

We have recently been in the unhappy situation of having two patients in shock in our wards, with massive gastric or intestinal tract bleeding. Both of them were Rh negative, and we had only one transfusion of Rh negative blood in our blood bank. We were very fortunate, however, in having Dr. Witebski on our hospital staff, and after a hurried consultation with him, we arrived at the following plan.

He says (and we found it to be true in practice) that if you have an Rh negative patient who has never been transfused before, you can give that patient all the Rh positive blood that you wish for 72 hours, but after that period of time you run a very grave risk, and the risk is more grave with each transfusion.

Many patients who are Rh negative do not become sensitized very readily when given Rh positive blood, and if they have been sensitized in the past with Rh positive blood, they may have lost that sensitivity. A good bacteriologic department can tell you whether your patient has been sensitized, so it may be possible—even though your patient has received Rh positive blood in the past—to give him some Rh positive blood during his present hemorrhage.

I think all of this boils down to the fact that if we have a limited amount of Rh negative blood, and don't know how many transfusions we are going to have to give these patients, we had better save the Rh negative blood, and transfuse them as much as we wish for 72 hours with positive blood. Try to have the issue settled, the surgery over, or, if the medical people insist on keeping the patient, make them promise to have the patient stop bleeding within 72 hours. If they have to have transfusions after that, you will have to give them Rh negative blood.

DR. FRANK H. LAHEY: It is my desire to discuss only one point in this excellent paper of Dr. Hinton and, as has been stated by Dr. MacGuire, it is an important one. That concerns itself with the attitude that all duodenal ulcers should be removed when a subtotal gastrectomy is done.

At various meetings I have discussed the desirability of removing the ulcer in subtotal gastrectomy for a duodenal ulcer, not because leaving the ulcer does any

harm, but because in so many of the cases it is not possible to do a safe inversion of the duodenum without removing the ulcer.

I am a little fearful that any statement that all duodenal ulcers should be removed might prompt men who have not had a large experience with them to remove some that would get them into trouble in the process of resecting them.

So that no one thinks my criticism applies to anyone else, I would like to say that I do not particularly worry about the younger surgeons attempting removal of duodenal ulcers that should be left in. I only have to speak of my own mistakes. More than once I have started out to resect a duodenal ulcer eroded into the head of the pancreas and adherent to the common duct, and before I had completed the operation, have wished I had not started the removal of the ulcer but had done some more conservative procedure.

The mortality of subtotal gastrectomy for duodenal ulcer is not related to the subtotal gastrectomy. It is related to the duodenum, particularly in the technical difficulties of removing duodenal ulcers and obtaining good closure of the duodenal stump when the duodenal ulcer is not removed.

I am not particularly anxious to refer to my earlier suggestion of the use of the T tube to demonstrate the presence and relation of the common duct to adherent duodenal ulcers but it is of great value and gives one great comfort, particularly when the sphincter is dilated and the tube can be passed into the duodenum. It then gives one information as to how low the level of entrance of the common duct is and how much duodenal stump one has between that point and the ulcer.

I know of nothing which is so distressing as to have mobilized a duodenal ulcer, having cut off that section of the duodenum in which the ulcer is, and then find that the common duct and pancreatic duct enter on the very edge of the remaining stump. This has occurred to me and has necessitated the transplantation of these ducts, an undertaking which, I believe, is extremely hazardous.

One of the first steps of all subtotal gastrectomies for duodenal ulcers, in my opinion, is the demonstration of the common duct at the point where it passes behind the duodenum. By this means one may make the decision as to whether the ulcer can be removed safely so that a good duodenal stump can be turned in or some more conservative procedure such as gastro-enterostomy with vagotomy should be done.

Regarding the whole discussion, I would like to say that I am old enough to have lived through many of these discussions about duodenal ulcer. While I would like to agree that I have learned a great deal in this discussion, I would still like to say that following this one I find the problem still far from standardized, and one which could still leave one quite confused.

DR. HAROLD D. HARVEY: I should like to speak very briefly on Dr. Moore's careful and thoughtful study of the cases of duodenal ulcers at Massachusetts General.

At Presbyterian Hospital, under Dr. St. John, we conducted a somewhat similar study, a few years ago, and we turned up with very comparable figures. We felt that 85 per cent of the cases treated by definitive surgery—which, in this case, were all gastrectomies—were satisfactory.

Dr. Charles Flood, meanwhile, had studied the cases treated only by medical regimen. The cases he studied, however, were different from Dr. Moore's, in that they were all cases that had been sick enough to be admitted to the hospital. He found that only 25 per cent of those remained satisfactory.

In any statistical study of this kind we must remember that there are certain pitfalls. One in particular, in duodenal ulcer, is that in many cases we have no objective criteria by which to judge the follow-up status of the patient; we have to rely largely on what he tells us.

An example of that appeared in the study made by Dr. Swenson of 2500 so-called normal stomachs by x-ray, in which he found a very appreciable number of deformed duodena which were indistinguishable from those that had deformities due to ulcers,

yet the patients said they had never had any ulcer symptoms. The reverse is also true. We often hear a patient complaining, when we must say to ourselves that we can see no objective reason why he should.

Nevertheless, on the basis of these follow-up studies, when they are carefully done, I think we now can say to the individual patient—and it is always the individual to whom we have to speak—"If you want to get rid of your ulcer symptoms for good, your best chance is to resort to surgery. And you can do this safely now. The lowering of postoperative mortality, which is now very low, indeed, and the overall safety of gastric surgery for peptic ulcer, have been among the distinguished features of recent surgery."

DR. LESTER R. DRAGSTEDT: I should like to report the presence of ulcers in certain of these experimental animals with totally isolated stomachs. This, I believe, is important, because in this instance we have the gastric mucosa subjected to the digestive action of pure gastric juice, unmixed with food or with regurgitated duodenal content.

On a previous occasion I have reported before this group that animals provided with a totally isolated stomach—to which the vagus nerves have remained intact—have displayed typical peptic ulcers in the isolated stomach. We have 21 such ulcers in our laboratory. Similar totally isolated stomachs from which the vagus nerves have been divided have never displayed an ulcer. That was also the experience of Dr. Ivy and his group with a large number of such preparations.

When we make a totally isolated stomach with the antrum anastomosed to the esophagus, so that we have preserved both the antrum and nervous phases of secretion, almost invariably a typical ulcer develops in the isolated stomach within a very short period of time, so it is very difficult to use this preparation for study for any long period of time.

The totally isolated stomach with the vagus nerves divided secretes small amounts of gastric juice and is usually free from ulcer. If, however, we then transplant the antrum from such an isolated stomach into the colon, or into the duodenum, and set up a hypersecretion of gastric juice in the vagotomized, isolated fundus pouch, we find a high incidence of perforating ulcers. It is quite apparent that the appearance of ulcers in the isolated stomach is not referrable to the presence or absence of vagus nerves in themselves, but is due to the rate of secretion by the isolated stomach.

Now, how do these experiments bear on the clinical problem? I am persuaded that the old dictum, "No acid, no ulcer," is correct. Does that also mean, "Some acid, some ulcer"? Obviously, it does not.

I have seen a large ulcer in the ileum produced by 2 sq. cm. of gastric mucosa in a Meckel's diverticulum. We don't know whether the ectopic gastric mucous membrane in Meckel's diverticulum is innervated by the vagus nerves or not. No one has ever demonstrated secretory fibers to this heterotopic mucosa. We know, however, that it responds to gastric and to the humoral agents that stimulate gastric juice. Does this mean that in all ulcer patients we have to take out every square centimeter of the fundus mucosa? Clearly, I think it does not.

If we believe our medical colleagues—that upward of 75 per cent of duodenal ulcer patients are treated satisfactorily by medical management—then we must agree that total abolition of acid in the gastric content during the entire 24-hour period is not necessary, because no one can claim that any internist secures complete neutralization of the gastric content for the entire 24-hour period, for the duration of the patient's life.

It has always seemed to me that in this problem, we have to consider both the aggressive action of the gastric content and the resistance of the mucosa. The aggressive action of the gastric content is due to the pepsin hydrochloric acid of the gastric juice and is greater when there is more gastric juice in proportion to food, saliva, and other neutralizing materials.

I think it is clear now that the secretory abnormality in duodenal ulcer patients is a hypersecretion of gastric juice in the fasting stomach, and an excessive response

of the fundic mucosa to the normal stimuli of gastric secretion, gastrin, food, alcohol or histamine.

We know that this hypersecretion of gastric juice in duodenal ulcer patients is neurogenic in origin. It is abolished by complete vagotomy. It would seem to me, then, in considering this problem, that patients with duodenal ulcer should be treated first by the internist, because he can cure or control a certain proportion of them. Those that prove refractory should be treated by the surgeon by the most conservative procedure that is at his disposal.

Since the major pathogenic factor in duodenal ulcer is hypersecretion, and since this hypersecretion is of cephalic or nervous origin—it is not of antrum origin, nor of intestinal origin—then the argument is clear that the physiologic operation for duodenal ulcer is either a vagotomy or the administration of a drug like Banthine, which depresses the nervous phase of secretion. Gastro-enterostomy should be coupled with vagotomy to simplify postoperative management and lessen gastric stasis. I cannot imagine how one can call resection of the stomach a physiologic procedure.

Dr. J. William Hinton (closing): I am very grateful to Dr. MacGuire for opening this discussion and questioning the removal of the ulcer "in toto."

If we are going to clarify our bad results in operations for duodenal ulcers, one must state clearly whether the ulcer was removed when the original resection was performed.

The figures that have been presented are not prohibitive as to mortality, and those were done in a city hospital, to a great extent. The mortality that results from the secondary operation, if the ulcer is left in situ, should be attributable to the first operation.

I am not concerned about the mortality in the hands of the young surgeon because the residents with long training have a lower mortality than many older surgeons because we are training them how to remove the ulcer "in toto."

I have received considerable encouragement from a patient reported by Dr. Sara Jordon some four years ago before the New York State Medical Society. If I do not have the data completely accurate I hope Dr. Lahey will correct me. This patient had a subtotal resection with the ulcer left "in situ" and developed a gastrojejunal ulcer within two years. Then for some ten or 12 years he had three or four massive hemorrhages. He had at least one revision gastrectomy with the development of a second gastrojejunal ulcer. Finally after about 12 years, with removal of the duodenal ulcer "in toto" his gastrojejunal ulcer immediately healed and he had a satisfactory end-result at the time Dr. Jordan reported the case two years later.

We had in our series three cases with spontaneous choledochoduodenal fistula and five with clinical jaundice from chronic pancreatitis, and those cases obviously represent advanced stages of the disease.

I am convinced from my experience that it is much easier, technically, to remove the ulcer which apparently looks hopeless when first exposed, than it is to remove some of the less advanced lesions, because the marked fibrosis around the advanced lesions gives a better line of cleavage.

In the bleeding ulcer, if you are going to get the most satisfactory results, one has got to have the courage of his convictions and remove these lesions "in toto" or have many patients die later from another hemorrhage which can be attributed to incomplete surgery. In the past three years, since the residents have been doing all of these operations, there hasn't been one instance of duodenal fistula.

Dr. Francis D. Moore (closing): I would like to thank the essayists and discussers for a most interesting symposium, and would like to add just one or two brief points.

Just as he finished his talk, I believe Dr. Glenn mentioned that 5 per cent of his patients, his ulcer patients, were being operated upon in his hospital. I wonder if he meant that figure, or if it was a typographical error. Certainly, in our experience, it

is much higher, and Heuer's series, from the New York Hospital, was around 12 per cent. Ours ran 20 per cent in our own hospital. When we follow them up and add the definitive surgery done somewhere else—which we wouldn't have known anything about—we find that 25 per cent of our patients are being operated upon.

As to the removal of the ulcer, there is no correlation whatsoever in our group between the result and whether or not the duodenal ulcer is left in, but there is a very high correlation between the result and whether or not all of the antral mucous membrane has been taken out. We believe that there is confusion in the literature on this important point. Many cases have been recorded in which a jejunal ulcer has been cured by the removal of gastric antrum left in at the time of the initial subtotal gastrectomy. We are not aware of any authenticated cases in which a jejunal ulcer has been cured by the removal only of a small additional portion of the duodenum not containing gastric mucous membrane. This confusion arises from the use of the term "resection for exclusion"; this term has unfortunately been used indiscriminately to include operations in which the gastric antrum was left in as well as those in which the duodenum was divided distal to the pylorus but the ulcer was left in. We feel that this confusion can be resolved by avoidance of the term "resection for exclusion" and the use of specific statements as to whether or not the gastric resection included the entire lower stomach and a full 360 degrees for the pyloric muscle.

Many of the papers have concentrated on surgical failures, which we should do, I am sure, in a surgical meeting. However, we also have to look at the medical disasters in this disease. I believe that the nicety of future ulcer care lies in undertaking definitive surgery in the right cases before enough failures have accumlated to justify the term, "intractable." This is a diagnostic problem, a problem in making the diagnosis of a progressive, virulent ulcer disease.

The old statement—attributed, I believe, to one of the members of this society—that "Surgery should only be undertaken after nine separate, complete and permanent medical cures," must be revised. Although the cat has nine lives, there is an end to the patient's patience.

Dr. John D. Stewart (closing): I don't find differences of opinion about the best method for treating acutely, massively bleeding ulcers unreasonable. In fact, I think it is entirely fair and proper that there should be differences of opinion. After all, why should we feel that any one method of treatment would be best applied throughout the country? It seems to me the obligation is for each surgeon and each clinic to obtain the best possible results with the patient.

It is quite clear that the facilities in clinics will vary. The volume of material coming in to clinics will vary, and the nature of the cases will vary. I think that point has been brought out very well by Dr. Bowers. It does seem to me, however, that each surgeon is obligated to appraise his methods very fairly, and is obligated to set up criteria which can be respected by others, and which can be tabulated over a period of time, and he is obligated to draw the right conclusions therefrom.

If there is any doubt in a given clinic as to the best method to be applied with respect to any surgical problem, I would suggest that the method of alternate cases—after definite scientific criteria have been set up—be followed until some sort of logical conclusion can be reached. The necessity for studying these patients carefully in the acute phase of severe hemorrhage should be apparent to all of us. I am sure that one of the reasons for differences of opinion from clinic to clinic—with respect to value of the methods—is that we are talking about different conditions.

It can be shown without any difficulty that in the acute phases of hemorrhage and during the onset of hemorrhagic shock, there may be, for hours, little or no correlation between the red cell count and the hemoglobin values. By means of vasoconstrictive shunts, and delay in hemodilution which sometimes go on over a period of six, eight or ten hours, the measurement of concentrations alone may prove very misleading.

Therefore, I believe that any comparison of results using different therapeutic methods must be based on very accurate studies of the particular cases.

DR. RALPH F. BOWERS (closing): Dr. Paine touched upon one of the points that I wished to make before my time elapsed. After examination and the period of observation begins by medical people and surgeons together, a 48-hour deadline is established similar to Dr. Paine's suggestion. The surgeons feel it is their responsibility to state the necessity for surgery within the 48-hour period and we always require the medical observers to do the same thing. When the medical people want to ride past the 48-hours, the surgeons demand that the fellow must stop bleeding and recover from that particular bleeding episode.

This plan has proved to be very satisfactory, because it creates a demand for the best possible medical therapy in case operation is not employed early. I believe that in those institutions where there is a high mortality rate with the conservative trend, the medical therapy itself is at fault; at least that is what I think I have had an opportunity to observe. One point is certainly clear; whatever type of treatment is chosen, operative or nonoperative, it must be the finest possible if good results are to be expected.

To show you that we have not completely deserted operative therapy, attention is directed to the last slide, which briefly details the surgical treatment of 24 cases, all but one of which were operated upon during the interval phase.

Observations were made in these operative cases of all factors that might be concerned—not only blood pressure and the pulse—but response to replacement therapy, age, the type of individual concerned, his ability to remain well, the environment of home or job, the mental processes that might contribute to the production of his ulcer, etc. The interval is employed at a date when the patient can be considered as a "chronic ulcer case"—25, 30, 45 or 50 days past the cessation of the hemorrhage.

I have searched for a test tube that will prognosticate accurately and have not found it. Dr. Patterson called it the crystal ball. All of us, perhaps subconsciously, have some sort of pressure on us in 1950 to get away from what is known as clinical or surgical judgment; but I maintain that it cannot be done with safety to the patient.

DR. FRANK GLENN (closing): First, in answer to Dr. Moore, we have operated upon about 16 per cent of ulcer patients who have been presented to the clinic. Of that 16 per cent, our primary operation has given us a good follow-up on approximately 12 to 15 per cent. After doing secondary operations we have about 5 per cent—after everything we have done—that are failures. That is a very small percentage of failures of the original number treated medically and then surgically.

May I make one comment about the bleeding ulcer? It seems to me that we can gain a little perspective by simply recounting briefly our experience. Out of 309 gastric resections done at the New York Hospital in the past four years for peptic ulcer, the operation was done in 53 cases because of massive hemorrhage. By that I mean that they had massive hemorrhage at the time they arrived in the hospital, or developed it while they were in the hospital.

Of the 53 patients who were treated by gastric resection, only 15 of them were treated as emergency gastric resections, this having been done usually within a period of 48 hours, although there were two examples that were observed for a slightly longer period.

Finally, as to our general policy, which I think I glided over a little too rapidly in closing: Confronted with the necessity for a secondary operation, we think you should be sure that you do an adequate gastric resection. If that has been done, then the next procedure—in the present state of our experience—is that of a vagotomy, and when that fails, as it has failed in our hands, we are then tempted to do a total gastrectomy, which I realize is a radical procedure but which I believe is justifiable when you have operated upon a patient five or six times and still have bleeding from a marginal or jejunal ulcer.

HISTOPLASMOSIS*

A COMMON CAUSE OF APPENDICITIS AND MESENTERIC ADENITIS

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THE EXHAUSTIVE STUDY of the genesis of appendicitis presented by Wangensteen in 1939[1] has directed attention to lymphoid hyperplasia as a common cause of appendiceal obstruction with resultant acute, subacute, recurrent and chronic appendicitis. During our recent studies[2] of benign gastro-intestinal histoplasmosis in children it became apparent that this cause of lymphoid hyperplasia was of importance in production of abdominal symptoms in all age groups, and that the organisms could be demonstrated in a significant percentage of surgical specimens.

Since the first descriptions of histoplasmosis by Darling in 1906,[3] attention has been focused upon the rare generalized fatal disease, summarized by Parsons and Zarafonetis in their review of 71 cases in 1945.[4] Recent extensive studies by Christie, *et al.* at Vanderbilt University[5-7] and by Palmer and associates of the USPHS,[8-14] correlated occurrence of pulmonary calcification with positive histoplasmin skin sensitivity tests, and established histoplasmosis as a common benign disease of wide geographic distribution, with greatest incidence centering in the confluence of the great mid-continental rivers. Later reports indicate a worldwide incidence.[15-16] During the past year Emmons and co-workers have demonstrated a large animal reservoir in rodents in Virginia and Georgia,[17-19] and have been successful in isolating *Histoplasma capsulatum* from the soil for the first time.[20] Our studies in children have established a common childhood disease with demonstration of the organisms in diseased tissue of the gastro-intestinal tract.[2]

Failure to recognize the organisms in reticulo-endothelial cells of lymphoid follicles has been due in part to the ready acceptance of the "tingible korporchen" of Flemming (1885) as nuclear debris,[22] and of Latta's description of lymphocytic fragments in the lymphoid tissues of the intestine of rabbits.[23]

The other major factor delaying recognition is the difficulty encountered in culturing the offending organism. Twenty-eight years after Darling's description, DeMonbreun succeeded in culturing it from a case of the generalized fatal disease.[24] Other successful cultures have been obtained in the generalized disease where large numbers of organisms have been present. Several positive cultures have been reported in cases that have recovered, and in the case reported by Kunstadter, *et al.*, growth first appeared after seven weeks of incubation.[25] Howell[26] states that in transferring cultures in the laboratory,

* Read before the American Surgical Association, Colorado Springs, Colo., April 21, 1950.

50 million viable spores must be inoculated into a single culture medium to insure growth.

The recognition of intracellular organisms in lymphoid tissue, aided by special stains, and development of technics for the laboratory demonstration of delicate mycotic organisms, have enabled us to establish benign histoplasmosis as a common disease of childhood and have led us to postulate that it is an important factor in appendicitis and mesenteric adenitis.

MATERIAL AND METHODS

The material studied consisted of surgical specimens from cases of appendicitis and of mesenteric adenitis in the Henry Ford Hospital files for a ten-year period, and of similar current specimens received from the operating room. These specimens were grouped in pathologic categories as: acute appendicitis, chronic appendicitis, normal and miscellaneous conditions of the appendix, and mesenteric adenitis. Studies of material from the files were morphologic and were accomplished by use of routine hematoxylin and eosin stains, and of special stains for organisms. The special stains employed were the Giemsa, Bauer's moderation of the Van Gieson, Gram-Weigert, Ziehl-Neelson, and Rawson's modification of the acid fast stain.[21] Current material was studied morphologically, culturally, and by animal inoculation.

A total of 2135 cases of appendicitis were encountered in the ten year review at Henry Ford Hospital; 1173 acute appendicitis, 768 chronic appendicitis, and 164 normal and miscellaneous conditions. Material from 30 cases clinically diagnosed as mesenteric adenitis were reviewed in this category. Twenty-one current cases, 13 of acute appendicitis, and eight of chronic appendicitis were examined. One case of mesenteric adenitis was encountered during the period of study.

Morphologic study of current material was the same as on filed material. Cultural studies were made of the macerated mucosa and submucosa following bacterial sterilization employing enriched media incubated at 30 and 37° C as advocated by Howell[26] and using the modification of Sabouraud's media suggested by Emmons.[18] This inoculum was also injected in chick embryos and in mice.

Cultures were observed for developments of a budding yeast at 37° F and of an aerial mycelium composed of septate hyphae producing the typical tuberculate chlamydospore at 30° F. Chick embryos were observed for any abnormality of growth, and for growth of a budding yeast. Mice were watched for symptoms of disease, and were sacrificed at five weeks. The descriptions of the histopathology of histoplasmosis in rodents by Emmons, *et al.*,[18] were used as reference in study of the mice at autopsy. In addition to the granulomatous lesions Emmons described, we were impressed by the lymphoid hyperplasia of reactive pattern in the presence of organisms as seen in human cases.

RESULTS

Of the 1173 cases of acute appendicitis, portions of 1049 were adequate for close scrutiny and 58 cases were diagnosed histoplasmosis. Thirty-five

of the 768 cases of chronic appendicitis and ten of the 164 normal and miscellaneous cases contained demonstrable Histoplasma. In 13 of 30 cases of mesenteric adenitis the organism was satisfactorily demonstrated (Table I). In addition, a uniform histologic picture was noted in the involved cases, consisting of a marked lymphoid hyperplasia, with prominent lymphoid follicles, and broad germinal centers containing scattered large macrophages giving the "starry sky" effect of reactive hyperplasia. The organisms appeared in the cytoplasm of the large phagocytic cells.

TABLE I.—*Material Studied Morphologically, and Results.*

Number of Cases	Diagnosis	Histoplasma Present	Percentage
1173	Acute appendicitis	58	5
768	Chronic appendicitis	35	5
164	Normal and miscellaneous	10	6
30	Mesenteric adenitis	13	43
2135	Totals	116	5.5

The paucity of current material was evident, and the incidence outlined above explained it, but parallel positive results in identical material in the study in children warranted reporting these few correlating results without the long and uncertain delay necessary to accumulate further data. Of the 21 appendices subjected to complete study, one contained morphologically identifiable organisms, and material in this one appendix reproduced the disease

TABLE II.—*Clinical Picture Present in Cases Diagnosed as Histoplasmosis Morphologically*

Case histories reviewed	90
Symptoms of chronic disease	78
Pre- and postoperative fever	70
Recurrent abdominal pain	56
Recurrence of symptoms postoperatively	17
Chest x-rays performed	13
Pulmonary disease present	12
Tuberculin negative	9
Not tested	4

in mice. In culture at room temperature, a sterile mycelium was produced, which could not be successfully transplanted. The 20 cases not revealing the organism have served as a very adequate control, and furnished ample evidence that the findings outlined are not coincidental.

A single case of mesenteric adenitis encountered during the study period contained the organism in morphologic sections. A budding yeast grew in fair numbers in the yolk sac injected with ground lymphoid tissue. Material from the yolk sac reproduced the disease in mice. Direct injection of lymphoid tissue in the mouse also reproduced the disease. The yeast grew poorly on enriched artificial media at 37° C, and growth at room temperature has

been slight, with formation of a fine septate mycelium, but without spore formation.

Of the 103 cases of histoplasmosis diagnosed morphologically, 90 case histories were available for review. The review revealed a pattern of chronic disease very similar to that encountered in children, though slightly less prominent (Table II).

Fifty-six patients gave history of recurrent episodes of abdominal pain, for a period of one month to ten years, prior to operation. Seventy patients ran an unexplained low grade fever for five or more days following operation. Seventeen patients were seen for recurrence of symptoms following operation. Thirteen patients had chest roentgenograms. One of these was normal. Twelve showed hilar enlargement and pulmonary infiltration with calcification. Nine of these had negative tuberculin tests. Three were not tuberculin tested.

CASE REPORTS

Case 1.—An 18-year-old white student nurse was admitted in January, 1936, complaining of abdominal cramps of 24 hours' duration, nausea and vomiting. She had had two previous similar attacks one week and one month prior to admission. Physical examination revealed a well-developed, well-nourished, white female with a temperature of 99° F., right lower quadrant tenderness and rebound tenderness. The white blood count was 10,300 with 76 per cent polymorphonuclear cells. At operation the appendix appeared indurated, and there were enlarged lymph nodes along the terminal ileum and cecum. The postoperative course was uneventful except for concern for an unexplained daily temperature elevation to 99.6° F for 5 days. On pathologic examination a granulomatous lesion was found and was interpreted as tuberculosis. Chest roentgenograms revealed bilateral, extensive, parenchymatous infiltration, interpreted as tuberculosis. The patient was hospitalized for 13 months, although she remained symptomless. Repeated sputa and gastric washings failed to reveal acid fast bacilli. Tuberculin tests were not done. She was followed as an outpatient following discharge. She had recurrent attacks of abdominal distress and was re-admitted in 1939, at which time an abdominal laparotomy was performed. At operation a thickening and induration of the terminal ileum was found and mesenteric lymph nodes were markedly enlarged. Pathologic examination of a mesenteric node revealed a marked reactive hyperplasia without evidence of specific inflammatory disease. Following this operative procedure she was admitted twice, in 1941 and 1942, for partial intestinal obstruction that responded to conservative measures. Chest roentgenograms revealed little change from the original films, with small areas of calcification appearing over a period of years, and grave doubt was cast on the original diagnosis. Following her discharge from the hospital she was married and had two children without complication and has worked full time as a nurse for six years. Review of histologic material revealed yeast-like organisms in small numbers in the granulomata of the appendix, and in larger numbers in macrophages in the enlarged follicles of the mesenteric lymph nodes.

Case 2.—A 21-year-old white student nurse admitted to the hospital complained of persistent abdominal pain of 3 weeks' duration, most severe in the right lower quadrant. She had been nauseated and vomited several times during this period. She gave a history of recurrent attacks over a period of three years. Physical examination revealed right lower quadrant tenderness with mild rebound tenderness. The white blood count was 10,250. At operation the appendix appeared scarred, surrounded by

fibrous adhesions, and there was enlargement of mesenteric nodes. Pathologic examination of the appendix showed a marked lymphoid hyperplasia, and moderate increase in submucosal fibrous tissue (Fig. 1). The postoperative course was complicated only by an unexplained low-grade fever persisting for five days. A chest roentgenogram revealed enlarged hilar shadows and calcification. The tuberculin test was negative. Review of the sections from the appendix revealed the presence of a small, spherical, acid-fast organism in large reticulum cells of the prominent lymphoid follicles.

Case 3.—A 61-year-old white male admitted to the surgical service, complained of lower abdominal pain of 24 hours' duration, nausea and vomiting. He gave a history

FIG. 1.—Low power view of wall of the appendix showing marked reactive lymphoid hyperplasia.

of recurrent similar attacks for a 6-year period. Physical examination revealed muscle spasm and marked right lower abdominal tenderness and rebound tenderness. The white blood count was 16,000. At operation a gangrenous appendix was removed. Pathologic examination revealed areas of gangrene and proximal lymphoid hyperplasia. Following operation the patient ran an unexplained low-grade fever. Chest roentgenograms revealed enlarged and calcified hilar lymph nodes. The tuberculin test was negative. Re-examination of the appendix revealed in the areas of lymphoid hyperplasia recognizable intracellular yeast organisms that varied from 1 to 6 micra in diameter and were acid fast (Fig. 2).

Case 4.—A 56-year-old white male was admitted to the hospital complaining of abdominal pain of several months' duration. He had had a gastrojejunostomy 20 years before as treatment for a chronic duodenal ulcer, and an appendectomy 12 years prior to admission for acute suppurative appendicitis. On physical examination there was central and right upper abdominal tenderness. On roentgen ray examination several opaque shadows were present in the region of the gallbladder and were interpreted as gallstones. At operation several stones were found and cholecystectomy was performed. A generalized mesenteric adenitis was found, and a lymph node was excised for histologic

and cultural examinations. The postoperative course was uneventful except for a low grade fever with temperature elevations to 100° F for 14 postoperative days. Microscopic sections of the lymph node revealed a reactive hyperplasia and the presence of organisms morphologically identified as *Histoplasma capsulatum*. Macerated tissue from the lymph node cultured in brain-heart infusion broth at 30° C produced a sterile mycelium that failed to produce spores in 6 weeks. Similar material inoculated in the yolk sac of a chick embryo caused death of the embryo at 18 days, and showed a growth of a small budding yeast (Fig. 3). This yeast produced a sterile mycelium at room temperature and showed scanty growth of the yeast form at 37°. Mice, inoculated intraperitoneally with tissue emulsion from the lymph node, showed reduction in growth and lethargy and were sacrificed at 5 weeks. There was marked splenomegaly and hepatomegaly. A reactive hyperplasia of lymphoid tissue of the gastro-intestinal tract, with accompanying Histoplasma infection were found (Fig. 4). The spleen contained a number of epithelioid granulomata as described above (Fig. 5). Mice injected with the yeast from the chick yolk sac showed an identical gross and microscopic picture.

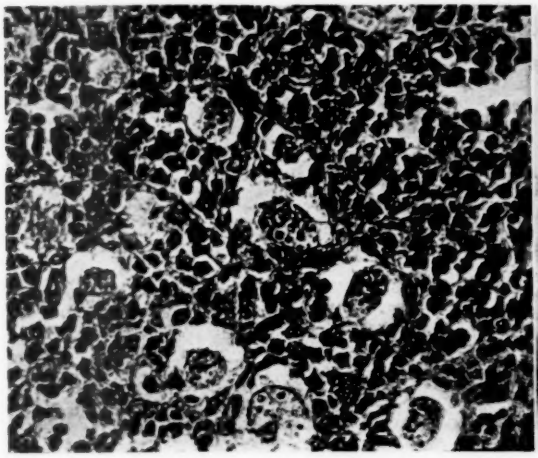

FIG. 2

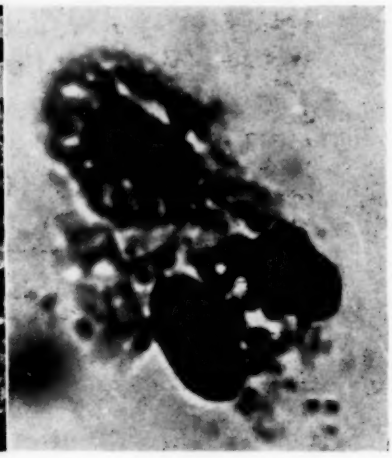

FIG. 3

FIG. 2.—High power view of reticulum cell containing Histoplasma capsulatum.
FIG. 3.—Yeast bodies from yolk sac culture.

DISCUSSION

This survey of 2135 surgical specimens revealed organisms morphologically identified as *Histoplasma capsulatum* in 103, or 5 per cent of cases. The presence of organisms was associated in all cases with a marked lymphoid hyperplasia. The significance of this infection in appendicitis was immediately apparent, and while clinically it most often was manifest as acute or recurrent acute appendicitis, the frequency of chronic appendicitis caused us to revise our concept of this disease as expressed in 1931,[27] and recognize a common specific infection causing chronic inflammatory disease of the appendix, which had a definite symptomatology and was a frequent important causal factor in the more readily recognized acute disease.

Of even more significance was the finding of organisms in 13, or 43 per cent of 30 cases of mesenteric adenitis. In all cases of mesenteric adenitis

encountered at operation a lymph node should be biopsied and cultured as was the single current case reported. Positive diagnosis will often explain chronic gastro-intestinal symptomatology. The results of culture of the

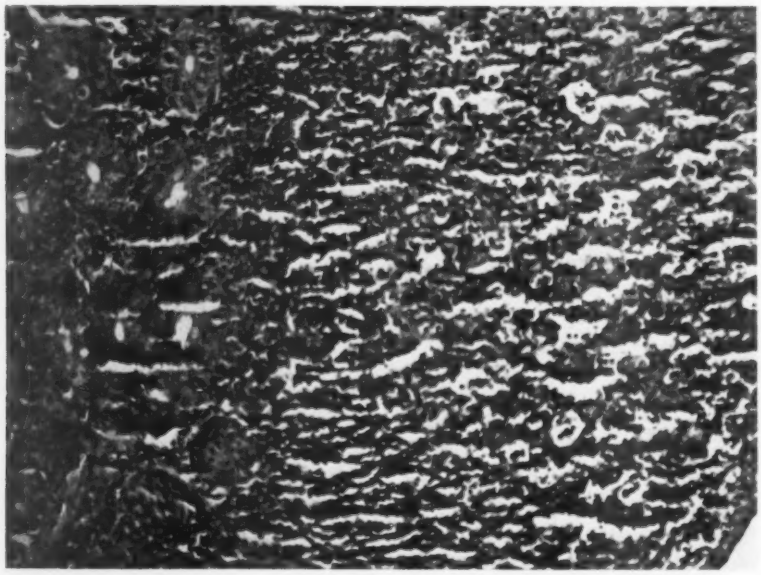

FIG. 4.—Low power view of wall of mouse intestine showing reactive lymphoid hyperplasia and presence of yeast organisms in large macrophages.

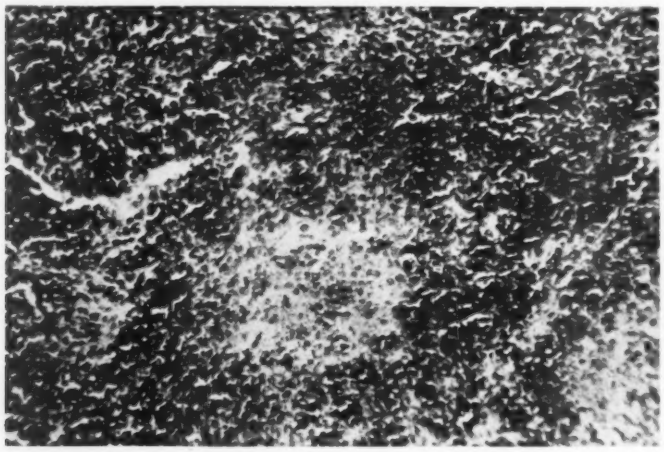

FIG. 5.—Epithelioid granuloma in mouse spleen.

organism from tissue were not disappointing, since previous work had indicated the difficulties to be expected. Demonstration of a delicate yeast at 37° C that grew as a Mycelia sterila at 30° C was considered significant. Re-duplication of the picture in mice in morphologically positive cases was

uniform and has suggested itself as the method of choice in demonstrating the organism. The close correlation between these results and results obtained in prior studies[2] enhances their value.

The clinical picture revealed by review of case histories is one of low-grade chronic disease, characterized by recurrent abdominal discomfort, low grade fever, acute exacerbations of abdominal pain, frequent pulmonary infiltration and hilar enlargement with negative tuberculin skin reaction. The case reports emphasize this clinical picture and indicate the value of recognition of the disease entity and correct diagnosis.

SUMMARY

A total of 2135 cases of appendicitis and mesenteric adenitis were reviewed, revealing a 5 per cent incidence of histoplasmosis in appendicitis and 43 per cent incidence in mesenteric adenitis. Histoplasmosis causes a lymphoid hyperplasia and by this mechanism is a cause of chronic and acute appendicitis.

The organism was demonstrated morphologically, culturally and by duplication of the disease in mice.

Review of clinical histories revealed affected cases to suffer from a low-grade chronic disease.

Case reports are presented and discussed.

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ACUTE APPENDICITIS III

AND ANALYSIS OF ONE THOUSAND AND THREE CASES*

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IN 1938 LEHMAN AND PARKER[1] reviewed 1069 cases of acute appendicitis occurring consecutively at the University of Virginia Hospital during the five-year period 1933–1937, and made a detailed analysis of all cases of localized peritonitis. They concluded that better results had been obtained in the latter by conservative than by immediate operative treatment. Recently all cases of acute appendicitis occurring during the six-year period 1943–1948 were subjected to preliminary review and a substantial decrease in mortality rate as compared with that of the earlier series was reported.[2] This decrease was ascribed in part to the use of specific anti-bacterial agents, *i.e.*, the sulfonamides, penicillin and streptomycin, without discounting other factors of improved therapy. It was believed that the combination of factors which had resulted in this decrease in mortality rate might also have altered the choice of conservative versus operative treatment of appendiceal peritonitis, both localized and diffuse. A more detailed analysis of the 1943–1948 series of cases was undertaken, and forms the substance of this report.

CLASSIFICATION OF CASES

In the first series reported from this hospital[1] the cases were grouped in three categories: (1) simple acute appendicitis, (2) appendicitis with abscess, and (3) appendicitis with diffuse peritonitis. Each class was accurately defined. In the present series, following a concept which has previously been outlined by Lehman,[3] a fourth group has been added: acute appendicitis with contaminated peritoneum but without established peritoneal infection, a group that in the first paper was included in Group I for reasons therein detailed. The following, then, is the classification used in the present series:

Group I—Simple Acute Appendicitis. This group includes all cases in which gross and microscopic examination of the appendix showed acute appendicitis, including many cases of gangrenous appendicitis without perforation or other evidence of contamination of the peritoneal cavity.

* Read before the American Surgical Association, Colorado Springs, Colo., April 21, 1950.

Group II—Acute Appendicitis with Contaminated Peritoneum. This group comprises all cases in which there was definite evidence of contamination of the peritoneal cavity, but in which the subsequent course ruled out the presence of an established peritonitis, either localized or diffuse. By definition all cases in this group had uncomplicated postoperative courses. The group includes (a) cases in which there was gross or microscopic evidence of perforation of the appendix with peritoneal soiling, (b) cases in which cloudy fluid was found in the peritoneal cavity with a positive culture, (c) cases in which peritoneal contamination was incurred by surgical accident, such as the rupture of a tense, gangrenous appendix in the course of removal, and (d) cases in which contamination was not evident at the time of operation but in which later wound infection with coliform organisms gave evidence that contamination had been present. As noted above, cases of this type were classified as "simple acute appendicitis" in the earlier series. However, there are many cases in Group II which, without the benefit of modern therapeutic adjuvants, especially the antibiotics, might have progressed to localized or diffuse peritonitis, with classification in Groups III or IV. Most of the cases in Group II would have been classified by most authors as cases of peritonitis.

Group III—Appendicitis with Localized Peritonitis. This group includes (a) cases that presented at operation a localized collection of pus or an inflammatory mass, and (b) unoperated cases which on admission presented a characteristic clinical picture, *i.e.*, a typical history, sepsis, localized tenderness and a mass in the right lower quadrant discovered either before or after relaxation with anesthesia.

Group IV—Appendicitis with Diffuse Peritonitis. This group includes all cases presenting clinical evidence of peritonitis extending beyond the right lower quadrant.

It may be seen that Groups I and II together comprise all cases of acute appendicitis without established peritonitis, whereas Groups III and IV together comprise all cases with established peritonitis.

MATERIAL

The analysis is based on all cases of acute appendicitis admitted to the University of Virginia Hospital during the six-year period 1943–1948, a total of 1003* cases (Table I). Only those cases are included which, after appendectomy, were reported by the pathologist as showing microscopic changes of acute disease, or, if the appendix was not removed, presented a clinical picture upon which a positive diagnosis could be established beyond reasonable doubt. No cases of chronic appendicitis are included.

* The preliminary report[2] was based on 1005 cases, but on review two duplications in tabulation were found and therefore the series was reduced in number to 1003. This has necessitated only slight alterations in the mortality rates.

It is interesting that in this series a six-year period was necessary to furnish 1003 consecutive cases, whereas 1069 cases had occurred in the five-year period 1933–1937. This is possibly explained by the fact that during the war years, especially during 1944 and 1945, a large proportion of the male population in the age group most susceptible to appendicitis was away in military service (Table I). Slattery, Yannitelli and Hinton report a similar experience.[4]

Comparison of the distribution of cases among the various groups between the two series (Table I) shows that the relative incidence of localized peritonitis is considerably less in the later series (10.9 per cent to 17.0 per cent) whereas the incidence of diffuse peritonitis is considerably greater (7.9 per cent to 5.5 per cent). Peritonitis as a whole comprises 18.8 per cent of the

TABLE I.—*Distribution of Cases.*

Year	Group I Simple Appendicitis	Group II Contaminated Peritoneum	Group III Localized Peritonitis	Group IV Diffuse Peritonitis	Total
1943	142	15	17	10	184
1944	107	12	12	18	149
1945	102	7	24	10	143
1946	114	15	25	16	170
1947	118	19	15	17	169
1948	145	17	17	9	188
Total 1943–1948	728 (72.5%)	85 (8.4%) 813 (81.0%)	110 (10.9%)	80 (7.9%)	1003
Total 1933–1937	829 (77.5%)		181 (17.0%)	59 (5.5%)	1069

1943–1948 diagnoses as compared with 22.5 per cent of the 1933–1937 diagnoses. In view of the probability as already stated that many cases of contamination in the later series were protected from the development of established peritonitis by the use of antibiotics and chemotherapy, it is believed that the difference of 3.7 per cent in the incidence of peritonitis between the two periods does not represent an important decrease in the severity of the disease as it appears in this clinic, and is responsible only to a negligible degree, if at all, for the improvement in results of treatment.

Age Distribution. The age distribution of all cases, by decades, together with the mortality rate for each decade, are shown in Figure 1. As expected, the preponderance of cases falls in the second and third decades. The progressive increase in mortality rate in the fifth, sixth and seventh decades is also predictable. The absence of mortality in patients above 70 years of age is not significant because of the small number of cases. However, it is noteworthy that no deaths occurred in the numerically large group of children ten years of age or under. Eight of these patients were two years of age or less, and six of these eight were critically ill with localized or diffuse peritonitis at the

time of admission. The youngest patient was five months old and the oldest "over 90."

Duration of Symptoms. The mean length of time between the onset of symptoms and admission to the hospital for each group of cases is shown in Table II. The implications of these figures are apparent. In general, when seen early, within 24 hours of the onset of symptoms, the disease process is likely to be confined to the appendix. With further delay the danger of contamination of the peritoneum increases, and the risk of an established

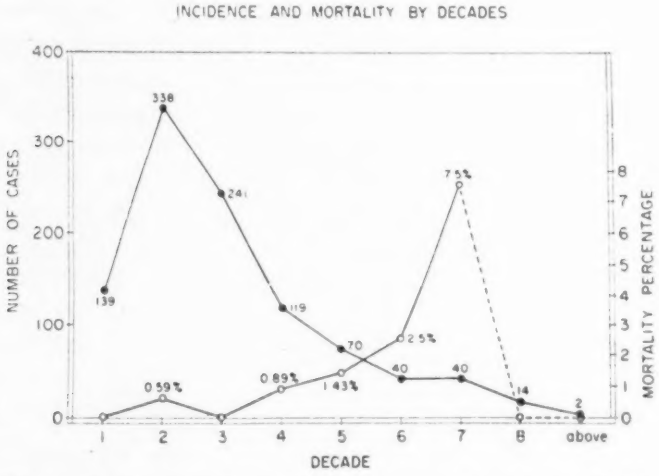

FIG. 1.—Incidence and mortality percentage of acute appendicitis by age decades.

TABLE II.—*Mean Duration of Symptoms Before Institution of Treatment.*

Group I	Simple appendicitis	23 hours
Group II	Contaminated peritoneum	36 hours
Group III	Localized peritonitis	120 hours
Group IV	Diffuse peritonitis	55 hours

peritonitis appears. However, two points must be emphasized. Cases may occur with symptoms up to a week in duration in which the disease has progressed slowly and remains limited to the appendix. In this series there were two cases of simple acute appendicitis seen at five days, one at six days, and three at seven days after the onset of symptoms. On the other hand there may be fulminating cases in which an established diffuse peritonitis is found soon after the onset of symptoms. In this series 18 cases of diffuse peritonitis presented symptoms of 24 hours' duration or less; one of these was at 14 hours, one at 12 hours and one at nine hours. The cases which were classed in Group III, Localized Peritonitis, were first seen much later than those in the other groups, averaging five days after the onset of symptoms. This reflects to some degree the resistance of the patient to his infection.

CLASSIFICATION OF TREATMENT

All cases in Groups I and II were subjected to immediate operation and in each case the appendix was removed. In Groups III and IV, treatment fell into one of the following programs:

1. *Immediate operation.* Appendectomy was carried out as a part of the majority of these procedures, while in others only drainage of an appendiceal abscess was effected. No attempt has been made to distinguish between "forced" and "elective" operations, as was done in the earlier study.[1]

2. *Conservative treatment begun; operation performed later.* In most cases the later operation consisted of drainage of an intraperitoneal abscess, usually without removal of the appendix. However, also included in this classification of treatment are a few cases of appendiceal abscess treated conservatively and discharged from the hospital only to be re-admitted in a few days or weeks with a recurrence of acute symptoms; in some of these appendectomy was performed rather than simple drainage. The choice between appendectomy and simple drainage was determined by the clinical status and the local pathologic findings at operation in the individual case. Again no division into "forced" and "elective" operations was attempted, partly because of the smaller amount of material, and partly because the reviewer was not always able to make the distinction from the data on individual charts.

3. *Conservative treatment begun; no operation.* The cases included here fulfilled the requirements for the diagnosis of localized or diffuse peritonitis, and in none was operation performed, except for interval appendectomy. In most of these cases complete subsidence of sepsis and complete disappearance of a mass were observed.

DETAILS OF TREATMENT

Conservative Treatment. The principles of expectant treatment are well-recognized and have been outlined in a previous paper.[1] At the time of that report chemotherapeutic and antibiotic agents and much present knowledge of fluid, electrolyte, and protein requirements and of blood volume replacement were not available. This knowledge has been employed as it has become available. Whole blood, plasma, and protein hydrolysates have been utilized extensively. Gastric or intestinal decompression with the Wangensteen suction apparatus has been used whenever indicated. Stimulants of intestinal motility, such as Pituitrin and Prostigmine, have been used only rarely in the treatment of peritoneal infection. In established peritonitis and in the immediate postoperative day or days in cases of contaminated peritoneum, complete deprivation of both water and food by mouth is considered a highly important factor in treatment.

Specific Anti-bacterial Therapy. The sulfonamides were in general use at the beginning of this series; they were employed extensively during the years 1943–1945 and to a less extent in 1946 but were used infrequently in

1947 and 1948. Sulfanilamide was used locally and sulfadiazine systemically. Penicillin was first used for appendicitis in selected cases in late 1943 but was not available for general use in adequate dosage until 1945. During the years 1946–1948 it was used extensively both by intraperitoneal and systemic administration, alone or in combination with other agents. Streptomycin was first used in October, 1946, and was employed with increasing frequency after that time in the acutely ill cases. As has been noted in the preliminary report on the present material,[2] the variations in choice of drug and route of administration are so great that analysis of the effect of each drug independently or of each combination of drugs is not feasible. One fact considered possibly significant, however, is that no death occurred in this series after streptomycin became available for use. There were 416 consecutive cases without a death; of these, 70 were cases of either localized or diffuse peritonitis, and of the 70, there were 43, in general the sickest patients, who received streptomycin in combination with penicillin and occasionally sulfadiazine.

Operative Treatment. A muscle-splitting incision of the McBurney type was used in 797 (86.25 per cent) of the operated cases. A right rectus incision, either muscle-splitting or retracting, was used in 127 cases (13.7 per cent), while a midline incision was used once. Occasionally a rectus fascia extension of the McBurney incision was necessary for adequate exposure. The choice of incision is not considered in this hospital to be of major importance. However, it should be noted that duration of hospitalization averaged two to three days less with the McBurney than with the right rectus incision.

Spinal anesthesia was employed in 712 (77.05 per cent) of the operated cases. In 18 of these cases supplementation with a general anesthetic was necessary. General inhalation anesthesia (some combination of nitrous oxide, oxygen, and ether) was used as the primary agent in 212 cases (22.9 per cent), while in one case local (procaine) anesthesia was used in combination with an inhalation anesthetic.

Early ambulation, usually within the first 24 hours after operation, was carried out in practically all cases of simple acute appendicitis. When peritoneal contamination or infection was present, patients were made to stand and walk as soon as the decline of sepsis and local signs indicated probable control of the infection.

Drainage of the peritoneal cavity after removal of the appendix was carried out in one case in Group I (simple appendicitis), in ten cases in Group II (contaminated peritoneum), in 22 cases in Group III (localized peritonitis), and in 17 cases in Group IV (diffuse peritonitis). Drainage of the wound down to the level of the peritoneum was used in two cases in Group II, three cases in Group III, and 11 cases in Group IV. Peritoneal drainage was used in 13 cases subjected to primary operation but without removal of the appendix. The only indication recognized by this service for drainage is the presence of granulation tissue with a localized collection of pus. Obviously this principle has been ignored in a small number of cases.

In contrast to the series reported by McGraw,[5] in which a step-by-step routine operative technic was rigidly adhered to, there has been no set procedure in this hospital for locating, delivering, and removing the appendix. Seven members of the attending staff have operated on the private cases, which constitute less than half of the total number, while the ward cases have been operated on by a large number of house officers. Many minor variations

TABLE III.—*Mortality.*

	Simple Appendicitis			Appendicitis: Peritoneal Infection											
				Localized			Diffuse			Total			Total		
Series	Cases	Deaths	Mortality %	C.	D.	M.%	C.	D.	M.%	C.	D.	M.%	C.	D.	M.%
1943 to 1948	813	2	0.24	110	0	0.0	80	6	7.5	190	6	3.1	1003	8	0.8
1933 to 1937	829	2	0.24	181	9	5.0	59	24	40.6	240	33	13.7	1069	35	3.27

in technic have occurred. In the great majority of cases, however, the appendiceal stump has been ligated, treated with phenol and alcohol, and buried in the cecal wall by a silk purse-string suture. When this has not been possible, as when the cecum was indurated or edematous, the ligated stump has usually been covered with a fat tag or piece of omentum.

RESULTS

Mortality. Table III shows the mortality rates for the period 1943–1948 compared with those of the earlier series, 1933–1937. All Group II (Contaminated Peritoneum) cases in the 1943–1948 series have been placed under simple appendicitis in order to make possible comparison with the earlier

TABLE IV.—*Mean Number of Days of Hospitalization Per Surviving Patient.*

	Number of Cases	Mean Number of Days
I. Simple appendicitis	726	4.5
II. Contaminated peritoneum	85	7.7
III. Localized peritonitis:		
Immediate operation	35	15.7
Conservative treatment begun; late operation	20	30.8
Conservative treatment begun; no operation	53	12.8
IV. Diffuse peritonitis:		
Immediate operation	61	18.1
Conservative treatment begun; late operation	6	46.8
Conservative treatment begun; no operation	7	22.1

series in which this combination was presented. This procedure does not alter the mortality rate of simple appendicitis materially, since there were no deaths in Group II.

In the simple appendicitis group, one of the two deaths was due to the anesthetic and the other resulted from an unyielding adynamic ileus without peritonitis, as demonstrated at a second exploratory operation.

* This table, with the exception of minor changes necessitated by the already noted correction in total figures, has already been published.[2]

Length of Hospitalization. The mean number of days of hospitalization for surviving cases in Groups I and II and with each method of treatment in Groups III and IV is shown in Table IV. Two cases in Group III are omitted as unsuitable: one, a case in which an appendiceal abscess was discovered and left undisturbed when the patient was operated upon for carcinoma of the rectum, and the other the case of a psychopathic individual who left the hospital against advice so that treatment was not carried out and the case was not followed.

TABLE V.—*Number of Complications Per Patient.*

Complication	Simple Appendicitis	Contaminated Peritoneum	Localized Peritonitis			Diffuse Peritonitis			Total
			Imm. Oper.	Conservative Treatment Late Oper.	Conservative Treatment No Oper.	Imm. Oper	Conservative Treatment Late Oper.	Conservative Treatment No Oper.	
Residual RLQ mass	0	4	2	2	7	10	3	2	30
Pelvic abscess	0	0	4	3	0	16	2	1	26
Subphrenic abscess	0	0	1	3	0	5	2	0	11
Subhepatic abscess	0	0	1	1	0	1	1	0	4
Wound dehiscence	0	1	0	0	0	2	0	0	3
Hematoma of wound	3	0	0	0	0	0	0	0	3
Paralytic ileus	3	1	3	3	2	6	2	2	22
Intest. obstr. in acute phase	0	1	0	0	0	1	2	0	4
Intest. obstr. later	0	3	0	0	1	1	1	0	6
Gas gangrene	0	0	0	0	0	1	0	0	1
Actinomycosis of wound	0	0	0	1	0	0	0	0	1
Fecal fistula	0	0	0	0	0	1	3	0	4
Retained sponge in peritoneal cavity	1	0	0	0	0	0	0	0	1
Urinary infections	4	0	0	1	2	1	1	0	9
Parotitis	0	0	1	0	0	0	0	0	1
Cardiac complications, non-fatal	0	0	1	1	0	0	0	0	2
Pulmonary complications	2	0	2	0	0	1	0	0	5
Lower nephron syndrome	1	0	0	0	0	1	0	0	2
Thrombophlebitis	0	0	0	0	0	2	0	0	2
Total complications	14	10	15	15	12	49	17	5	137
Number of Patients	728	85	36	20	54	67	6	7	1003
Mean number of complications per patient	0.02	0.12	0.42	0.75	0.22	0.73	2.83	0.71	0.14

Complications. The complications which occurred in this series, both those directly related to appendicitis and those occurring incidentally, are listed in Table V for each group and method of treatment. The mean number of complications per patient is extremely low except in the single category of patients with diffuse peritonitis in whom late operation was performed after conservative therapy had been started; here it is 2.83 per patient.

Conservative versus Operative Treatment. The comparison of operative with conservative treatment in appendiceal peritonitis, both localized and diffuse, is given in Table VI. Here, in each group, all cases in which conservative treatment was begun are grouped together, regardless of whether or

not operation was performed at a later stage, and comparison is made with the cases treated by immediate operation with regard to (1) the mean duration of hospitalization in days, (2) the mean number of complications per patient, and (3) the mortality rate. In localized peritonitis the mortality rate for both forms of treatment is zero, and the mean duration of hospitalization and the number of complications show no important differences between the two forms of treatment. In cases of diffuse peritonitis, however, immediate operation resulted in a mortality rate, mean number of complications, and mean duration of hospitalization of only about one-half of that obtained with conservative treatment.

An attempt has been made to demonstrate statistical validity of the data presented. In the localized peritonitis material, the differences between the figures are minor and no statistical validation is possible. None of the differences in the results between non-operative and operative treatment of diffuse

TABLE VI.—*Comparison of Operative and Conservative Treatment in Appendiceal Peritonitis.*

	Localized Peritonitis		Diffuse Peritonitis	
	Immediate Operation	Conservative Treatment (All Cases)	Immediate Operation	Conservative Treatment (All Cases)
Number of cases	35	73	61	13
Mean number of days of hospitalization per patient	15.7	17.7	18.1	33.5
Mean number of complications per patient	0.42	0.37	0.73	1.69
Mortality rate (per cent)	0	0	6.15	13.3

peritonitis have statistical significance on account of the small number of instances of conservative treatment and the wide deviation of individual figures from the mean.

DISCUSSION

Since earlier detailed analysis is available in the localized peritonitis group[1] and not in the diffuse peritonitis group, the interpretation of the data presented must be first discussed in the two groups separately. The question may be asked how it happens that approximately one-third of all cases of localized peritonitis in the 1943-1948 series (Table VI) were treated by immediate operation during a period when the conservative treatment of this condition was considered at this hospital to be superior on the basis of the previous study. Undoubtedly errors in preoperative diagnosis accounted for a few of the instances. Some of the operations may have been performed because of developing opinion that immediate operation combined with the employment of antibiotics was presenting as good results as conservative treatment. This is fortunate, for it provided the opportunity for comparison of the two methods under modern conditions.

Unfortunately, however, the differences in grouping in the localized peritonitis material between the 1933-1937 series and the 1943-1948 series make

accurate comparison between the results of each method of treatment under older and present therapeutic conditions impossible. In the earlier series the distinction between "elective" and "forced" operation, which seemed at that time both possible and logical, furnished data that showed for the most part statistically significant differences in the results of operative and non-operative treatment respectively. On the basis of these figures it was judged that non-operative treatment in localized peritonitis was the treatment of choice. The data furnished by the present analysis, however, in which for the reasons noted the distinction between "elective" and "forced" operation is not made, furnish no such clear-cut grounds on which to base a conclusion. Operative and conservative treatment appear to have given approximately equal results.

In the diffuse peritonitis group, immediate operation appears to be twice as effective as conservative treatment but the figures lack statistical significance. However, it should be noted that over four-fifths of the cases of diffuse peritonitis were treated by immediate operation (Table VI) and that the decrease in over-all mortality in this group when the two series are compared is greater than the decrease in mortality of the entire material. The 1943–1948 mortality for diffuse peritonitis is about one-fifth of that of 1933–1937, whereas the mortality of the entire material in the later series is about one-quarter of that in the earlier series (Table III). This may indicate that a large preponderance of choice of immediate operation in these cases has not been harmful.

The question whether all cases in which a diagnosis of acute appendicitis has been made should be subjected to immediate operation regardless of the stage of the disease must be reconsidered on the basis of the present data. This question has been the subject of controversy for many years. A survey of the German literature of the past 20 years on this subject was recently published by Goepel,[6] and his own views presented, but this review is of interest chiefly from a historic point of view as it is based on experience without the use of modern antibiotic agents. In this country, McGraw[5] has recently advocated immediate operation in all cases judged able to withstand operation. His mortality during the ten-year period of 1938–1947 of 0.64 per cent in 1411 cases of appendicitis at the Henry Ford Hospital, only 2 per cent of which were treated conservatively, lends weight to his thesis, especially since he had no deaths in the last five years of his series. Zinninger, reporting with Tashiro[7] in 1946 on 936 cases of appendicitis at the Cincinnati General Hospital, and more recently, discussing the paper of McGraw,[5] also emphasized the importance of immediate surgery. On the other hand, Schultz,[8] reporting on cases of perforated appendicitis from the Milwaukee Children's Hospital, emphasized the importance of non-operative treatment in those cases with obvious perforation. Likewise, Thieme,[9] analyzing 1042 cases of suppurative appendicitis from the St. Joseph's Mercy Hospital, Ann Arbor, Michigan, during the years 1936–1944, with a corrected mortality rate of 2.6 per cent in the first five-year period and 1.1 per cent in the second five-year period,

credited conservative treatment as a factor in the decreased mortality second in importance only to the use of the sulfonamides. However, both of the latter reports deal with cases treated prior to the general use of penicillin and streptomycin.

Although the question of conservative versus immediate operative treatment of appendiceal peritonitis must be decided on the basis of mortality and morbidity, yet immediate operation has certain indirect advantages. Conservative therapy does not remove the diseased appendix, which therefore remains as a potential source of future trouble. In this series ten patients who were treated conservatively on their original admissions were subsequently re-admitted with acute symptoms and had further periods of hospitalization. Although all patients treated conservatively were warned of the likelihood of future attacks and were given appointments for interval appendectomy, of those who did not develop acute symptoms only 50 per cent actually returned as directed. The remaining patients presumably still have their appendices and are potentially subject to future attacks.

Difficulty in the exact diagnosis of the stage of appendicitis, even in the most expert hands, is not infrequent, particularly in cases in which a vague right lower quadrant mass is thought to be present. The experience of every surgeon includes instances in which the mass is found at operation to be not an abscess but omentum or agglutinated small bowel around an acutely inflamed but unruptured appendix, which can be removed with impunity. Thus, by immediate operation, with the modern therapeutic adjuncts, some cases may remain in the contaminated peritoneum group which might otherwise eventuate in localized or diffuse peritonitis.

In addition, cases are encountered occasionally in which an unsuspected condition such as carcinoma of the cecum may be found at operation, and, although resection may be deferred at this time because of lack of preparation of the bowel, yet the facts that a definite diagnosis has been made, and that definitive treatment will be promptly instituted, offer a better prognosis than if the mass had been treated expectantly on the presumptive diagnosis of appendiceal abscess. There are therefore at least three advantages of immediate operation if one ignores possible differences in morbidity and mortality.

As already stated, the differences in morbidity and mortality are not statistically significant. On the basis of their apparent meaning, however, support is suggested for a changed point of view in regard to the treatment of appendiceal peritonitis from that expressed in 1938.

In localized peritonitis, it is probably justifiable to operate immediately, at least in the earlier cases. In cases of several days' duration, with a sharply localized firm mass, it may still be wiser to treat without operation for a day or so to see whether spontaneous improvement is occurring. Instead of waiting sometimes many days for this to take place, as was advocated earlier, it is probably wise now to expose the area in all cases in which prompt improvement is not obvious.

In diffuse peritonitis, the policy seems somewhat clearer than it did when the 1933–1937 material was studied. There is a suggestive basis for adopting a policy of immediate operation in these cases as the first choice, as compared to the former adoption of expectant treatment as the first choice.

In neither localized peritonitis nor diffuse peritonitis are these changes in point of view so solidly based that one can be sure of the correctness of the policies expressed above. We have been able to find no conclusive statistically controlled data in the literature on these points. The decision in any case must be made on the basis of the individual picture presented. The present conclusions must be regarded only as statements of policy and not as rules of procedure. It is expected that in time sufficient data will accumulate to permit statistical evaluation of the wisdom of the policies.

The present report is the only one that could be found from a clinic previously advocating conservative therapy for localized appendiceal peritonitis in which a detailed study has been made in the attempt to determine whether modern therapeutic adjuvants may have made advisable a change from this program.

SUMMARY AND CONCLUSIONS

1. An analysis of 1003 consecutive cases of acute appendicitis from the University of Virginia Hospital occurring in the years 1943–1948 has been presented, and in part compared with an earlier series of 1069 cases in the years 1933–1937.

2. Gross mortality statistics as repeated from a preliminary review of the 1943–1948 material, already published, show that the total mortality is 0.8 per cent as compared with 3.27 per cent for the 1933–1937 series. The data do not suggest a material difference in the severity of the disease as presented during the two periods under consideration. In the preliminary report the decrease in mortality was ascribed in part to chemotherapy and antibiotic agents, especially streptomycin.

3. The differences in the results of conservative and operative treatment in localized peritonitis are minor.

4. Immediate operation in diffuse peritonitis appears to be twice as effective as conservative treatment, but this difference is not statistically significant.

5. On the basis of these data no definite conclusions can be formulated as to the choice between immediate operation and conservative treatment of appendiceal peritonitis under modern conditions, which include the newer methods of support of the sick patient and the employment of chemotherapy and antibiotics. The data suggest, however, that under these conditions further experience may show superiority of immediate operation over conservative treatment.

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DISCUSSION.—DR. HOWARD C. NAFFZIGER: With reference to the presentation from Dr. McClure and his associates, it is worthy of note that re-study of old material in our pathologic files is often illuminating in the light of our most recent knowledge.

I should like to report here another infestation which is not related to histoplasmosis, but yet is not too dissimilar in its manifestations—namely Toxaplasmosis Gondii. This protozoan infestation was first reported in a human being by Janku in Czechoslovakia in 1923 and re-study of certain pathologic specimens of ours have indicated that this infection was present in California in that same year.

We do not know how it is transmitted. There is an occasional grouping of the appearance of the severe, acute form of the disease in the neonatal group, and this is of particular interest to the neurologic surgeon.

At a recent clinical-pathologic conference we discussed four neonatal cases, two of which were born on the same day in San Francisco. These newborn cases are not difficult of recognition, if microphthalmia, chorioretinitis, and enlargement of the head with minute calcifications, evident on radiologic examination, are kept in mind. A yellow ventricular fluid with a tremendously high protein content is associated with it.

This conference and these cases stimulated in me a recollection of a similar infant that came under my care in 1923 and a search revealed that pathologic material had been preserved from that autopsy. In the light of our present knowledge, a re-study of it revealed infiltration of toxoplasma in the retina and the central nervous system, associated with extensive visceral changes in heart, liver, spleen and other organs. Both parents have now been shown, 25 years later, to have positive skin tests and also that they are both positive to the toxoplasma neutralizing antibodies.

The age of these patients is usually related to the severity of the lesions, infants being those most intensely affected. Lesions tend to regress in the extraneural viscera and progress in the central nervous system and its appendage, the eye. In the brain the basic lesion is the microglial nodule.

The mothers who bear these children who are infected transplacentally prior to birth, have not shown recognizable clinical evidence of any disease during gestation. It is likely that the mother receives the primary infection during the pregnancy. The children of later pregnancies may show no evidence of it, even though the mother has the latent form persisting, as shown by skin tests and serologic findings.

In the subacute and more chronic forms, chorioretinitis, minute intracranial calcification and involvement of the central nervous system should bring this disorder to mind.

These unsual infections with histoplasmosis and the protozoan toxoplasmosis, if kept in mind, will no doubt be recognized with increasing frequency.

Dr. Willard H. Parsons: My remarks will be confined to the paper of Drs. Lehman, Hawks and Becker. The essayists have reviewed two series of patients, each almost identical in number and each cared for in the same institution under parallel circumstances. It appears that there was a definite lowering in the mortality and morbidity rates in the group of patients treated by immediate surgical intervention.

Dr. Lehman and his associates imply that the antibiotic and chemotherapeutic agents account for the improvement in their results. As a matter of fact it is perhaps true that this improvement was due in no small part to returning to the basic proposition that the offending agent, namely the appendix, was immediately removed. Here, as always should be the case, the antibiotics were employed as an adjuvant to, and not as a substitute for, indicated surgery.

I wish to discuss particularly the mortality incident to appendicitis when it occurs in individuals 60 or more years of age.

Years ago, perhaps before this Association, Mays drew attention to the very definite clinical differences in appendicitis occurring in those below and those above the age of 40 years. In the former, appendicitis is an ulcerative lesion of the mucosa generally relatively easily recognized and cared for. In the older person there is usually thrombosis of the vessels and the entire appendix is gangrenous. It perforates promptly, diffuse peritonitis follows, and there are posed great diagnostic and therapeutic problems.

If the individuals more than 60 years of age that are included in the group just reported by Dr. Lehman and his associates are removed from that group, the mortality rate, already enviably low, probably would still further be sharply reduced.

Recently I reviewed the records of 500 consecutive patients, all 60 or more years of age, on whom I had operated for one reason or another, and of this group about 8 per cent of the patients were operated upon for appendicitis. In every one of these patients the appendix at the time of surgery was gangrenous, had perforated, and there was diffuse peritonitis. In each instance antibiotics were given and just as promptly as possible the appendix was removed, with a mortality rate of less than 3 per cent, materially lower, I believe, than would have been the case had the so-called more conservative plan been followed.

I think the essayists are to be congratulated upon their contribution, for it is a valuable one. It is valuable because it pertains to a subject of great clinical importance. Appendicitis, while perhaps not too dramatic a disease, is nonetheless frequent in occurrence and is highly lethal in its results if improperly treated. Moreover, the individual who dies of appendicitis—and a great many do die of appendicitis—is quite as dead, and dead quite as permanently, as those far more rare individuals who succumb, for example, to the more glamorous coarctation of the aorta.

Dr. Thomas H. Lanman: I wish to discuss Dr. Lehman's paper, from the point of view of the younger age group. The cases I shall refer to are all under 12 years of age.

For many years, with Dr. Ladd, and now Dr. Gross, at the Children's Hospital, we have felt that the operative treatment of acute appendicitis in this age group is the more desirable method and will give better results. We feel that all these young patients, no matter how sick they may be when first seen, can be brought into condition for safe surgery in the space of a comparatively few hours.

Our series represents 836 cases of acute appendicitis. In this group the percentage of cases with rupture still runs between 50 and 60 per cent. In July, 1944, after 248 consecutive cases without a fatality, we had one death. This case we (being burdened with a New England conscience) include as a death, although death occurred some four months after the operation for the ruptured appendix and was due to a metastatic brain abscess. I think that this patient does not represent an "operative" death. Since then there have been 588 consecutive cases of appendicitis—still about 55 per cent were ruptured on admission to the hospital—with no deaths, and all were operated on within a few hours after admission.

We, therefore, feel it is important that we discard in our teaching the so-called "waiting policy," and we think it is particularly important to discard that teaching in such cases as were referred to by Dr. Becker; namely, those in which there is a diffuse peritonitis.

In many such cases you will find, as you all know, that the intestinal contents are pouring into the peritoneal cavity from the site of rupture. We feel that you must remove the offending organ. We feel that no amount of antibiotics or chemotherapy will ensure success without operation and usually drainage. Our figures seem to confirm this. We are unwilling to rely on antibiotics alone. (We did have a series of 90 consecutive cases even before sulfanilamide, with no deaths.) We feel, as Dr. Parsons has just said, that antibiotics are a very valuable adjunct, but that it is far more important to teach and to use the basic surgical principles for getting your patient ready for operation, and then to operate.

Dr. Frederick A. Bothe: Before discussing mortality I wish to say that before opening the abdomen I often experience difficulty in drawing a sharp distinction between the patient who has a localized peritonitis and the one with a spreading peritonitis. I am sure that all of us have had the experience of having made a preoperative diagnosis of a localized peritonitis, only to find a generalized peritonitis when the abdomen was opened. Though this distinction is not always possible, the patient's condition permitting, our results show that by not delaying operation the mortality is lower.

I wish to speak briefly on the findings of the Appendicitis Mortality Committee of the Philadelphia County Medical Society. Three years ago I reported an analysis of the first three-year period of the work of this committee. It represented the pertinent facts revealed in the analysis of the deaths that occurred in three years in 17 hospitals in Philadelphia. Eight of these hospitals were teaching institutions and nine were non-teaching institutions. I will not repeat all the findings reported at that time, but there were three facts which I wish to emphasize again, because they were very evident in our second three-year report. The first was patient's delay. I mention that because this delay was present in over 50 per cent of the fatal cases. We speak of not delaying the operation after getting the patient into the hospital. Should we not, by education, see that delay is either reduced or eliminated before the patient is hospitalized?

While this is primarily the patient's fault, there were some cases in which the physicians contributed to this delay. The second fact was that again approximately ten per cent of the deaths were due to embolism. Of this group, 25 per cent occurred after the patients had left the hospital. This fact should be considered when we attempt to tabulate the cardiovascular complications occurring in patients treated with early ambulation. These cases should be included if our statistics are to be accurate. The third fact pertained to the cardiac patient who was known preoperatively to be a severe cardiac. Again we found that these patients did not die within the first few postoperative days but usually between the eighth and tenth postoperative day. We felt this was significant and indicates the necessity of careful cardiac management over a prolonged postoperative period.

In the analysis of the second three-year period there was one new fact brought out which is worthy of brief consideration; namely, the mortality from appendicitis in the aged. The greatest number of deaths occurred in this group. Naturally we expect a higher mortality in aged individuals but the analysis revealed that over 50 per cent of these patients were admitted to the hospital in practically a moribund condition and did not have any operation. The findings at postmortem examination indicated that acute appendicitis was the cause of death.

When operation was performed, in 40 per cent of the cases this procedure was delayed from 30 to 40 hours. The study revealed that in some instances operation was delayed because of the poor general condition of the patient, such as extreme dehydration, marked disturbance in the electrolyte balance, etc., in others, because of difficulty

in arriving at the diagnosis. In discussing this group of deaths the committee felt that since we are living in the age when we are seeing more elderly patients we should consider acute appendicitis more seriously as the cause of abdominal pain in the aged if we wish to reduce this mortality.

Dr. McClure's paper on the evidence of histoplasmosis in mesenteric adenitis was most interesting. This presentation should afford a stimulus for many of us to look for the evidence of histoplasmosis in our future cases.

DR. ROY D. MCCLURE: This investigation started with morphologic and cultural demonstration of histoplasmosis in an appendix showing marked hypertrophy of the lymphoid tissue and functional obstruction. The presence of the organism has not been identified by the pathologists in the past, these spherical bodies having been considered nuclear debris.

A number of papers have been published on appendicitis through the years. From Fitz' first paper in 1866 until February, 1950, a total of 13,621 papers on this subject are listed. The peak years of publication were 1906 with 460 papers and 1931 with 480 papers; last year there were only 93 papers. So we have not reviewed the entire literature at this time, but we know that this is the first paper on this phase of the disease to be presented before this association, and one, we believe, of great importance in calling attention to a common specific cause of obstructive appendicitis and mesenteric adenitis.

I would like to call attention to an editorial published in the Journal of Surgery, Gynecology and Obstetrics for August, 1932, by Professor D. P. D. Wilkie, entitled "The Fatal Acute Appendix" in which he clearly differentiated appendicitis into a simple acute form with direct inflammatory involvement of the wall and into the obstructive type which we have in the past considered due to a fecolith, resulting in distention, gangrene, perforation and peritonitis. Wilkie gave credit for this differentiation to Van Zwaluwenburg of Riverside, California, in a work published about 38 years ago, in 1912. The role of lymphoid hyperplasia in obstructive appendicitis has been repeatedly emphasized since that time, and our demonstration of a specific organism as a cause of the lymphoid hyperplasia, implicates histoplasma as a cause of this very serious type of appendicitis.

We hope that this paper may stimulate careful morphologic and cultural search for histoplasmosis in specimens sent to the laboratories from the operating table.

DR. EDWIN P. LEHMAN: I want to thank the discussers for their interesting contributions.

To answer Dr. Bothe's question about our definition of localized peritonitis, the definition is simply a mass. If there is no mass and yet a peritoneal inflammation, it may be a contaminated peritoneum or the early stages of diffuse peritonitis, and its later course—and only its later course—will determine which it is.

I want to congratulate Dr. Lanman on a beautiful series of appendicitis in children. It usually seems my fate, when I present figures of which I am proud, to have one of the discussers present figures that are much better.

I want to make one other point clear, and that is that we do not ascribe the improvement in our results entirely to antibiotics; we consider them as one of the additions to our total protection of the surgical patient. Certainly, I do not believe that the difference in the number of cases which are operated upon immediately—that is, the choice of operation rather than expectant treatment—is responsible for reducing our mortality to a quarter of what it was ten years ago.

I think it might be interesting if I were to show one slide, the data of which have already been published, which shows how difficult it is to define in clinical material what one is accomplishing with chemotherapy and the antibiotics.

[Slide] This represents a study of 192 cases of peritonitis from the point of view of the use of antibiotics and chemotherapy.

There were 171 cases that received one of the four drugs shown, sulfanilamide, sulfadiazine, penicillin and streptomycin. The combinations, which include not only combinations of drugs but also combinations of methods of administration, systemic or local, were 17. The largest number of cases with one combination was 44, penicillin and sulfadiazine, both given systemically.

Obviously, of course, one cannot pick out any one of the drugs as being the most effective. The only suggestive evidence appears in relation to streptomycin. The first use of this drug was in October, 1946, and the last death in this series was in September, 1946, with 416 consecutive cases of all types without a death.

DR. ARTHUR B. MCGRAW: I think the conclusions of this paper by Dr. Lehman and his associates are of a special significance in view of the enthusiasm in some quarters for treating appendicitis primarily and solely with antibiotics.

When we saw this paper's abstract on the program, Dr. McClure and I recalled that in June, 1948, we had reported a comparable series of 1365 cases of appendectomy for acute appendicitis, from 1938 to 1947, with nine deaths and a mortality of ½ of 1 per cent. For the last five of those ten years there had been 559 consecutive appendectomies without mortality.

We thought, therefore, that it might be fitting to bring that experience up to date. For the years 1948 and 1949 we can add 231 more appendectomies for acute appendicitis, without mortality, making an overall operative mortality for the past 12 years of 0.4 per cent among 1596 cases, and of zero per cent in the last 790.

As to use of antibiotics in these 231 patients operated on for acute appendicitis in the last two years, three out of four of them were given either penicillin or streptomycin, and very frequently both. In the 165 simple appendectomies which would correspond with Dr. Lehman's groups 1 and 2, two out of three were given antibiotics. In the 66 serious and complicated cases, corresponding to Dr. Lehman's groups 3 and 4, every one was given antibiotics. Furthermore, four out of five of the 66 complicated cases were drained at operation.

We agree with Dr. Lehman that these antibiotic drugs are very definitely and extremely helpful adjuncts in the treatment of appendicitis nowadays, but they should not be used as a method of treatment in lieu of operation.

One possibly concealed factor in our low mortality rate has been the extreme care we have been using in the division of general surgery during the past four or five years in the early detection and treatment of thrombo-embolism.

We still hold that three factors come first in the matter of the treatment of acute appendicitis:

First, alertness in recognizing its symptoms and signs and reaching a diagnosis promptly. Second, to proceed with prompt operation once the diagnosis is made. Third, the consistent use of a standardized operative technic which is sound in its conception and in its detail, and which is safe both for the difficult and for the easy cases.

DR. ALAN RAFERTY (closing): Dr. Naffziger's comments on toxoplasmosis are very pertinent. We included toxoplasma among the organisms to be considered and differentiated in the morphologic identification. Demonstration of a definite capsule distinguishes histoplasma from toxoplasma. The cases we have encountered in children fell predominantly in an older age group with greatest incidence at ten years of age. The incidence curve was nearly identical to that of onset of sensitivity to histoplasmin noted in Public Health Service surveys. The youngest case encountered was an infant of six months, with an organism present identical to that confirmed by culture. There is no evidence that histoplasmosis is ever congenital.

DR. WALTER F. BECKER (closing): I wish to thank Doctors Parsons, Lanman, Bothe and McGraw for their comments. They are to be congratulated on the excellence of their results. I am grateful for the privilege of presenting this paper.

BLOOD VOLUMES IN NORMAL AND BURNED DOGS

A COMPARATIVE STUDY WITH RADIOACTIVE PHOSPHORUS TAGGED RED CELLS AND T-1824 DYE[1],[2]*

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SHOCK IN SEVERE BURNS now is recognized as due in large part to a decrease in the circulating blood volume. This was indicated first by the factual evidence of plasma exuding from the burn surface, by the apparent primary loss of plasma alone associated with a rising hematocrit and later by actual measurement of the plasma volume in the burn patient. For these reasons, clinicians focused their attention on replacing the apparent lost portion of the blood, that is, plasma. This treatment proved to be less than ideal for all severe burns. Therefore, investigations employing other intravenous therapeutic agents for severe burns were made both in the laboratory and in the clinic. These included various salt and colloid solutions, and whole blood.

Plasma loss in the burn patient has been estimated by the determination of plasma volume after injection of a known amount of dye (T-1824, "Evans Blue"); the decrease in the red cell volume, at the same time, has been calculated by means of the well-known plasma volume—venous hematocrit formula. Along with a loss of plasma, such studies showed an apparent decrease in the total circulating red cell volume soon after serious burns; replacement therapy which included both whole blood and plasma apparently gave gratifying results.[1, 2]

However, the reliability of plasma volume measurements by T-1824 and of red cell volumes calculated from the dye plasma volume and peripheral venous hematocrit in burns has been questoned. Comparison of the dye disappearance slopes in normal and burned animals enables one to determine whether there is an abnormal, rapid loss of dye from the blood stream following burns. Likewise, if one "tags" the red cell with radiophosphorus (P^{32}), the red cell volume in the burned animal or patient can be estimated directly by the isotope dilution technic. The simultaneous determination of plasma volume by the dye dilution method (T-1824) and the red cell volume by the tagged cell method (P^{32}), allows the estimation of error involved in the calculation of red cell volume by the plasma volume—hematocrit formula.

Studies with radioactive phosphorus and iron from this and other laboratories[3, 4, 5] have established the fallacious nature of red cell volumes calcu-

* Supported by a grant from the Medical Research and Development Board, Surgeon General's Office, Department of the Army. Read before the American Surgical Association, Colorado Springs, Colo., April 21, 1950.

† Acknowledgement is made of the technical assistance of Evelyn Hayes.

lated by the plasma volume hematocrit formula for *normal human subjects,* but such information was not available for the normal dog, as regards radiophosphorus. More importantly, the error involved in the calculation of red cell volumes by the dye-hematocrit method in the presence of a rising or high venous hematocrit, as commonly seen following severe burns, is not yet established.

Accordingly, the purpose of the present study has been to determine the validity of the plasma volume as estimated by the dye dilution technic (T-1824) in the burned dog and the validity of red cell volumes estimated by the use of the plasma volume peripheral hematocrit formula in the normal dog and following a standard 20 per cent burn associated with a high venous hematocrit. A single clinical example of the usefulness of actual knowledge of the circulating red cell volume as determined by the tagged cell method in one severely burned patient will be presented to illustrate the scientific basis for red cell infusions in severe burns in the presence of hemoconcentration.*

MATERIAL AND METHODS

Details of animal care, the burning procedure, and the red cell volume determination by radiophosphorus are available in other reports from this laboratory.[5, 6]

Healthy, mongrel dogs, whose weights ranged from 5.9 to 21.1 Kg. (average 12.6 Kg.) were studied before and after a standard 20 per cent deep second degree burn. The dogs were shaved one or two days before burning. Food was withheld for 15 hours prior to burning. The burns were produced with a thermostatically controlled burning iron, so regulated that application to the skin for one minute resulted in a deep second degree burn. The surface area of each animal was calculated by the formula of Cowgill and Drabkin and the iron applied the requisite number of times to produce a 20 per cent surface burn. The dogs were anesthetized with Nembutal (sodium pentobarbital), 30 mg./Kg., given intravenously.

The plasma volume was determined with T-1824 dye by the Gregersen technic as modified by Gibson and Evelyn.[7] The disappearance rate of the dye was calculated from the slope of the extrapolated dye concentration-time curve. The red cell volume was *calculated* from the T-1824 plasma volume and the peripheral venous hematocrit, the latter being corrected for occluded plasma by the factor 0.96. The formula used is:

$$\frac{\text{T-1824 Dye Plasma Volume} \times 100}{100 - (\text{Average Peripheral Venous Hct.} \times 0.96)}$$

= Blood Volume; Blood Volume — Plasma Volume = Red Cell Volume.

The red cell volume was also *measured,* rather than calculated, by the radiophosphorus technic of Hevesy, as modified by Nachman, James, Moore

* It should be mentioned that the present study is a part of a much broader and more intensive investigation underway in our laboratory and clinical wards on the fundamental mechanism involved in the anemia which follows surgical, radiation, and thermal injury.

TABLE I.—*Composite Data in Non-splenectomized Dogs Before and After a 20 Per Cent Second-degree Burn.*

Wt. in Kg.	Conditions	T-1824 Dye Disappearance Slope				Plasma Volume by T-1824 cc./Kg.				Plasma Volume by T-1824 cc./Kg. Difference			Peripheral Venous Hematocrit × 0.96				Red Cell Volume by T-1824 cc./Kg.				Red Cell Volume by P^{32} cc./Kg.				Red Cell Volume by P^{32} cc./Kg. Difference			Body Hematocrit R.C.V. by P^{32} / R.C.V. by P^{32} + P.V. by T-1824				Ratio Body Hct. / Venous Hct.				Ratio R.C.V. by P^{32} / R.C.V. by T-1824			
		C	B	27H	7.5D	C	B	27H	7.5D	B	27H	7.5D	C	B	27H	7.5D	C	B	27H	7.5D	C	B	27H	7.5D	B	27H	7.5D	C	B	27H	7.5D	C	B	27H	7.5D	C	B	27H	7.5D
18.2	C	.104				61.9							40.6				42.3				37.1							37.5				.924				.877			
	B		.038				47.6			−14.3				47.7				43.4				28.7			− 8.4				37.7				.790				.662		
14.1	C	.030				57.4							36.5				32.9				28.4							33.1				.907				.862			
	B		.019				34.0			−23.4				51.3				35.8				21.3			− 7.1				38.5				.751				.596		
11.4	C	.050				59.2							41.8				42.5				43.9							42.6				1.020				1.035			
	B		.080				34.6			−24.6				48.7				32.7				28.3			−15.6				45.0				.925				.866		
19.6	C	.025				59.3							38.8				37.6				36.5							38.1				.982				.970			
	B		.000				43.5			−15.8				53.4				49.8				33.2			− 3.3				43.3				.811				.666		
16.4	C	.092				56.2							45.5				46.8				50.7							47.5				1.045				1. 83			
	B		.000				40.5			−15.7				63.9				71.8				52.3			+ 1.6				56.3				.881				.728		
9.9	C	.117				61.1							37.0				35.9				35.1							36.4				.984				.977			
	B		.192				55.6			− 5.5				42.9				41.7				43.8			+ 8.7				44.1				1.029				1.051		
7.7	C	.225				50.8							34.9				27.1				30.0							37.1				1.064				1.105			
	B		.108				48.4			− 2.4				46.1				41.4				29.0			− 1.0				37.4				.812				.699		
20.7	C	.057				32.3							53.1				36.5				41.9							56.5				1.065				1.148			
	B		.055				21.0			−11.3				68.0				44.5				32.8			− 9.1				61.0				.897				.737		
21.1	C	.017				56.3							53.8				65.6				51.6							47.8				.888				.786			
	B		.142				32.6			−23.7				71.3				80.9				49.3			− 2.3				60.2				.845				.609		
8.6	C	.100				57.6							39.8				38.0				42.2							42.3				1.064				1.110			
	B		.000				35.7			−21.9				56.4				46.2				34.7			− 7.5				49.3				.874				.751		
7.5	C	.138				49.1							33.3				24.5				23.6							32.5				.977				.962			
	B		.000				46.0			− 3.1				35.9				25.7				1 .3			− 4.3				29.6				.825				.751		
11.8	C	.048				56.9							38.3				35.3				33.6							37.2				.971				.954			
	B		.109				46.5			−10.4				43.7				36.7				35.9			+ 2.3				43.6				.997				.995		
10.7	C	.019				45.0							48.4				42.3				47.3							51.2				1.057				1.116			
	B		.010				28.3			−16.7				67.4				58.5				35.8			−11.5				55.4				.822				.612		
	7.5D			.058				63.8			+18.8				37.4				38.2				37.5					37.0				.988				.980	
10.5	C	.119				49.6							51.2				52.0				43.1					− 9.8	46.5				.908				.830			
	B		.079				33.3			−16.3				67.1				68.0				40.7			− 2.4				55.0				.819				.598		
	7.5D			.026				80.2			+30.6				30.3				35.0				32.3					28.7				.945				.924	
12.7	C	.071				45.3							40.1				30.3				32.4					−10.8	41.7				1.039				1.068			
	B		.024				39.5			− 5.8				50.9				41.0				30.2			− 2.2				43.3				.850				.737		
	27H			.000				55.2			+ 9.9				39.4				35.8				31.9			−0.5				36.6				.929				.890	
	7.5D				.111				64.5							37.8				31.5				31.7			− 0.7				33.0				1.006				1.007

| | | |

and Evans[5] and adapted for use in the dog as follows: (1) Approximately 15 cc. of blood was drawn from an external jugular vein and placed in a vial containing a sterile solution of approximately 0.1 millicurie of radioactive phosphate and heparin. This was incubated and centrifuged, the plasma removed, and the cells washed and resuspended in saline; (2) After withdrawal of the control sample for the dye blank from an external jugular vein, 5.0 cc. of T-1824 (0.06 per cent) dye and 10.0 cc. of the radiophosphorus tagged cell-saline suspension (approximately 35 microcuries) were injected simultaneously. (3) In the great majority of experiments, blood samples were taken from the opposite external jugular vein at ten, 20 and 30 minute intervals and after centrifugation for 45 minutes at 3000 revolutions per minute were analyzed for red cell radioactivity and plasma dye concentration. (4) Aliquots of the tagged red cells not injected were diluted 1-250 before counting.

Control plasma and red cell volumes were done on 35 dogs, using T-1824 dye and radioactive phosphorus (P^{32}) simultaneously. Twenty dogs were burned approximately six days after their control study. Red cell and plasma volumes were determined simultaneously with P^{32} and T-1824 dye at the sixth post-burn hour, 27 hours after burning, and 7.5 days after burning. Red blood cell counts were done, and mean red cell corpuscular volumes were calculated on 12 dogs six days before and six hours after burning.

To control possible changes in the circulating red cell mass due to the contraction of the spleen, similar studies before and after burning were performed on eight dogs splenectomized two to three months previously.

In addition, red cell and plasma volumes were determined by P^{32} and T-1824 in five non-splenectomized dogs six days before and six and a half hours after the administration of intravenous Nembutal, 30 mg./Kg., to ascertain the role of the anesthetic in the red cell and plasma volume fluctuations following the burn.

The pertinent data were analyzed statistically by the Fisher "t" test.

RESULTS

The results are presented in Tables I, II, and III, and Figures 1, 2, and 3.

Plasma Volume. The disappearance slopes of T-1824 dye are similar in both the control and six hour post-burn experiments (Fig. 1). There was an average loss of 28 per cent of the plasma volume at the sixth hour post-burn. The plasma volume returned to normal by the twenty-seventh hour, and increased to 25 per cent above the control values by the end of the first week (Table I, Fig. 2).

Venous Hematocrit. At the sixth post-burn hour the peripheral venous hematocrit had risen, on the average, 33 per cent above the pre-burn level. By the twenty-seventh hour this had returned to normal and gradually decreased to 17 per cent below the control value one week following the burn. These changes in the venous hematocrit were not due to changes in the mean cor-

FIG. 1

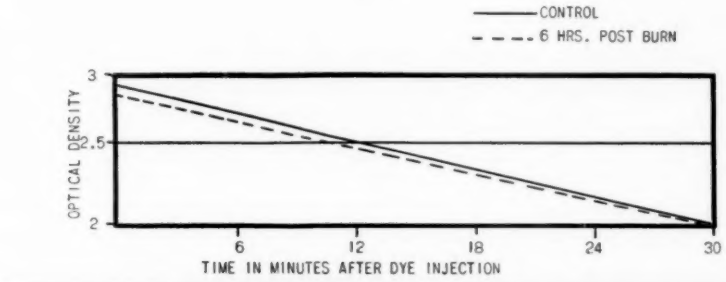

FIG. 2

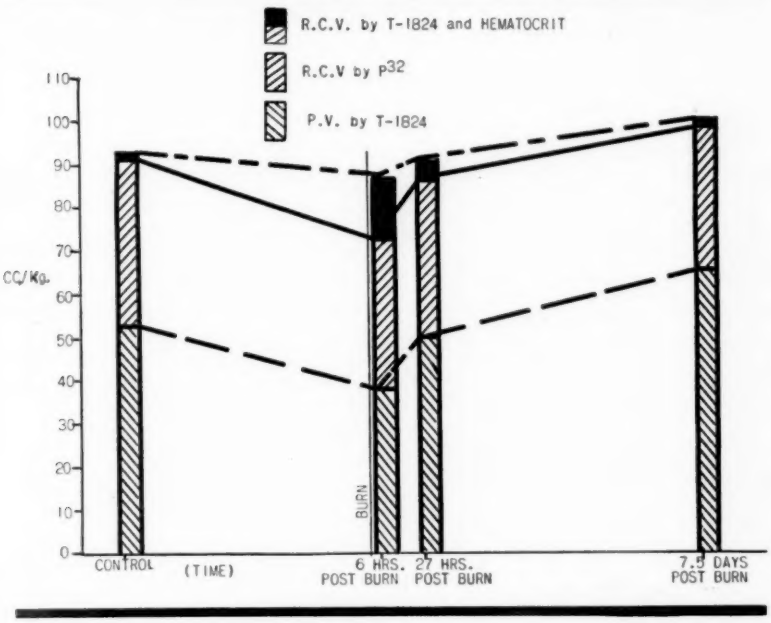

FIG. 3

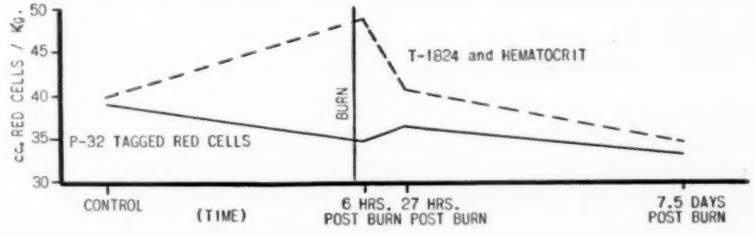

FIG. 1.—A comparison of the mean disappearance slopes of T-1824 dye in 35 control dogs and in 20 dogs six hours after a 20 per cent deep second degree burn.

FIG. 2.—A comparison of mean changes in the total circulating blood volume, red cell volume, and plasma volume in cc./Kg., as determined by T-1824 dye and radiophosphorus (P^{32}) before and after a 20 per cent deep second degree burn.

FIG. 3.—A comparison of mean changes in the red cell volume, cc./Kg., as determined by T-1824 dye hematocrit and radiophosphorus (P^{32}) before and after a 20 per cent deep second degree burn.

puscular red cell volumes, since these remained constant in all determinations (Table I).

Red Cell Volume. The control red cell volumes were very similar when determined simultaneously by radiophosphorus measurements and calculated by the dye plasma volume and venous hematocrit formula. Six hours following the burn, however, there is a marked discrepancy in the results of the

TABLE II.—*Data on Splenectomized Dogs Before and After a 20 Per Cent Deep Second-Degree Burn.*

Exp. No.	Wt. in Kg.	Conditions	Red Cell Volume by T-1824 cc./Kg.			Ratio R.C.V. by P^{32} / R.C.V. by T-1824		
			C	B	28H	C	B	28H
1	5.9	C	36.1			.897		
		B		44.7			.625	
		28H			30.8			1.044
2	15.9	C	34.1			.875		
		B		35.9			.883	
		28H			28.5			1.038
3	18.6	C	36.2			.970		
		B		39.8			.893	
4	10.5	C	29.2			.928		
		B		38.4			.754	
		28H			29.2			.919
5	13.9	C	43.7			.893		
		B		45.9			.752	
		28H			38.0			1.053
6	14.5	C	45.5			1.052		
		B		56.3			.905	
		28H			48.7			.975
7	13.6	C	22.5			1.007		
		B		33.8			.730	
8	12.5	C	41.2			.957		
		B		49.1			.740	
		28H			43.4			.843
Mean	13.2	C	36.1			.95		
		B		43.0			.79	
		28H			36.4			.98

C—6 days before burning
B—6 hours after burning.
28H—28 hours after burning.

two methods; that is, the *dye red cell value* at this time is 25 per cent greater than the P^{32} red cell value. (This difference is statistically significant, $p = 0.001$.) The discrepancy results from the fact that the "dye red cell volume" *increases* 22 per cent above the pre-burn level while the radiophosphorus red cell volume *decreases* 11 per cent. At the twenty-seventh post-burn hour, the red cell volumes as determined by both methods are essentially alike and continue to maintain this relationship at the one week determination. At this time, both the dye and P^{32} red cell volumes show a 15 per cent loss of red cells from the circulation (Table I, Fig. 3).

Blood Volume. The apparent total blood volume calculated by the dye method is only *6 per cent below* the control value six hours after the burn,

the plasma loss being counterbalanced by the apparent red cell gain. In contrast, the blood volume found by adding the dye plasma volume and the P^{32} red cell volume is *21 per cent below* the control values (Fig. 2).

Effect of Splenectomy. The eight splenectomized dogs showed the same specific changes in red cell volume relationship, as calculated by P^{32} and T-1824, as the non-splenectomized animals. Only at the sixth post-burn hour does a statistically significant discrepancy between the methods exist, and this is due in large part to an *apparent* red cell increase as calculated by the dye technic. The T-1824 disappearance curves and changes in plasma volume were essentially the same in both groups of dogs (Table II).

Effect of Nembutal Anesthesia. Plasma and red cell volumes done by both methods 6.5 hours after intravenous Nembutal, but no burning, showed no significant alterations as compared to the control experiments (Table III).

DISCUSSION

It should be emphasized that the basic principle underlying both the dye plasma volume and P^{32} red cell volume determinations is the dilution of the injected substance; that is, a known amount of the specific material is injected into the blood and the subsequent dilution by either plasma or non-tagged red cells reflects the volume of the plasma or red cell compartment. There has been considerable discussion as to the reliability of this general principle in shock. As Fine[8] so cogently states, the first or mixing part of the dilution may be markedly affected by the circulatory disturbances of shock, where red cell trapping, and a sluggish, even stagnated peripheral circulation, are present. The dilution of the tagging agent may be incomplete or delayed at this time because of inadequate mixing with the total anatomical blood mass. As a result, measurements of the *morphologic blood volume* will be in error. However, it would appear that the important clinical entity to measure by laboratory methods is the portion of the total blood volume which is *physiologically active*. From this point of view, the use of the dilution principle to measure the *physiologic blood volume* is not invalidated by possible delayed mixing of the injected tag with the total blood mass.

As far as the dye disappearance rate is concerned, the second phase of the dilution, there is the possibility that in burns and shock the T-1824 dye escapes more rapidly than normal from the vascular bed and that, consequently, the plasma volume would be incorrectly estimated. Evans,[9] and Noble, and Gregersen[10] have shown, however, that the disappearance rate of T-1824 in normal and shocked humans and dogs is identical. In the present study, the rate of escape of T-1824 from the blood stream is identical before and after burning. *No* increased rate of escape takes place at the sixth hour following a 20 per cent deep second degree burn in the dog.* It would ap-

* There is reason to suspect that in later experiments, when we increase the extent of the burn to involve 30 per cent and 40 per cent of the dog's body surface, we may well find more rapid loss of dye from the plasma.

TABLE III.—*Data Before and After Intravenous Nembutal.*

Exp. No.	Wt. in Kg.	Conditions	T-1824 Dye Disappearance Slope		Venous Hematocrit X0.96		Red Cell Volume T-1824 cc./Kg.		Red Cell Volume by P^{32} cc./Kg.		Ratio R.C.V. by P^{32} / R.C.V. by T-1824		Body Hematocrit		Ratio Body Hematocrit / Venous Hematocrit	
			C	N	C	N	C	N	C	N	C	N	C	N	C	N
1	10.9	C	.000		42.94		43.3		43.9		1.013		43.3		1.008	
		N		.020		39.55		39.7		38.6		.972		38.8		.981
2	12.7	C	.055		51.60		52.6		52.0		.918		51.3		.992	
		N		.080		46.88		39.9		46.3		1.059		50.6		1.079
3	11.1	C	.027		38.25		42.3		37.2		.879		35.2		.921	
		N		.056		41.53		42.3		45.1		1.068		43.1		1.038
4	13.4	C	.023		45.30		42.8		46.6		1.090		47.4		1.047	
		N		.000		57.53		54.6		57.0		1.045		58.6		1.018
5	19.3	C	.089		48.82		39.8		36.0		.904		46.3		.948	
		N		.014		46.28		34.2		33.4		.977		45.7		.988
Mean	13.5	C	.040		45.4		44.2		43.1		.96		44.7		.98	
		N		.034		46.3		42.1		44.1		1.02		47.4		1.02

C 6 days before Nembutal.
N 6.5 hours after intravenous administration of Nembutal, 30 mg./Kg.

pear, then, that the T-1824 dye technic for measuring plasma volume yields reliable information under the experimental conditions described. By utilizing this technic, there was demonstrated at the sixth post-burn hour an average loss of 28 per cent of the plasma volume, or 15 cc./Kg. of body weight. The plasma volume returned to the preburn level by the twenty-seventh hour, and increased to 25 per cent above the control values by the end of the first week. This last value contributes to a dangerous increase in the total blood volume and along with excessive use of whole blood and salt may be the necessary factor for the production of pulmonary and systemic edema at this time.[11, 12]

The calculation of red cell volume from the dye data involves not only the plasma volume but also the peripheral venous centrifuge hematocrit. If either of these are incorrect, the calculated red cell volume will be incorrect. It has been demonstrated here that the plasma volume measurement is apparently valid. The fault then, must be the error involved in the venous hematocrit. The hematocrit is a measure of the volume of red cells per unit blood and therefore will be affected not only by the number of red cells, but also by individual erythrocyte volume. Calculation of the mean red cell corpuscular volumes revealed no difference before or after burning, and therefore, the discrepancy in red cell volumes by the two technics cannot be accounted for on this basis.

When the hematocrit is used with the plasma volume in the calculation of the red cell mass, it is assumed that the peripheral venous hematocrit represents the body hematocrit, that is, the average hematocrit of the total circulating blood. (Body Hematocrit $= \frac{\text{R.C.V. by } P^{32}}{\text{R.C.V. by } P^{32} + \text{P.V. by T-1824}}$

There is ample evidence to indicate that such is not the case in shock. Gibson, Fine, *et al.*[13] have demonstrated that the *peripheral venous hematocrit is significantly higher than the true body hematocrit* in various types of peripheral vascular collapse. This is also true in the present study. Six hours after the burn, the observed peripheral venous centrifuge hematocrit is about 15 per cent higher than the body hematocrit. It is for this reason that the red cell mass, calculated from the plasma volume data is *too high* and exceeds the P^{32} red cell volume determination by 25 per cent.

This fact is of clinical importance. When the P^{32} method is employed, there is actually shown a *decrease* of 11 per cent in the circulating red cells at the sixth hour following the standard burn. At this time, not only does the dye red cell volume fail to show the decrease in the circulating red cell mass, but it may even show *an increase.* When this distorted, elevated red cell value is added to the plasma volume, the total blood volume will also be falsely estimated. The dye technic overestimated both the red cell volume and blood volume in the hemoconcentration phase following burns and does not yield accurate data to guide replacement therapy.

Mention has been made of an 11 per cent red cell loss as measured by the P^{32} method six hours following the burn. It can be expected that such red cell deficits will increase as the severity of the burn increases. This deficit may be the result of red cell destruction, trapping and stagnation, and, in practice, may be superimposed upon an already existing anemia. From the practical viewpoint in the treatment of burn shock, it is not important that this deficit may eventually be alleviated, in part, by subsequent mobilization of the intact, trapped red cells when the peripheral circulation becomes adequate. In the early post-burn period, the trapped red cells do not make a physiologic contribution; thus, adequate replacement therapy for severe burns demands the inclusion of red cells.

It should be noted that Nembutal anesthesia was not the factor which produced the observed red cell volume changes. In addition, the spleen cannot be incriminated as the factor which caused red cell volume changes, because the findings were essentially the same in splenectomized and non-splenectomized dogs.

CLINICAL APPLICATION

In order to demonstrate the clinical importance of the discrepancy between red cell volumes as determined by T-1284 and radiophosphorus, and to illustrate the magnitude of the immediate post-burn red cell deficit, the blood volume protocol of a single severely burned patient is presented.

This patient was a 29-year-old, previously healthy, Negro woman who was admitted shortly after receiving second and third degree flame burns involving 75 per cent of the body surface. The blood volume observations were made six and three-quarters hours after the burn, during a period of clinical shock and hemoconcentration. It will be seen (Table IV) that the ratio, $\frac{\text{R.C.V. by } P^{32}}{\text{R.C.V. by T-1824}}$ is 0.55; that is, the dye hematocrit red cell volume is 45 per cent greater than the corresponding P^{32} measurement. In addition, the dye red cell value is 4 per cent above the estimated normal red cell volume, while the P^{32} red cell measurement shows a *43 per cent deficit*. The blood volume, when calculated entirely from the dye data, is only 31 per cent below

TABLE IV.—*Summary of the Blood Volume Protocol of a Burn Patient. (O.J.B., M.C.V. No. 78149)*

Plasma volume:	Estimated normal P.V.	=3208 cc.
	Observed P.V.	=1356 cc.
	Per cent change	= −58 per cent
Red cell volume:	Estimated normal R.C.V.	=2467 cc.
	Calculated R.C.V. (T-1824 and Hct.)	=2587 cc.
	Measured R.C.V. (P^{32})	=1413 cc.
	Per cent change by the calculated T-1824 R.C.V.	= +5 per cent
	Per cent change by the measured P^{32} R.C.V.	= −43 per cent
	Ratio $\frac{\text{R.C.V. by } P^{32}}{\text{R.C.V. by T-1824}}$	=0.55
Total blood volume:	Estimated normal B.V.	=5675 cc.
	Calculated B.V. (T-1824 P.V. +T-1824 Hct. R.C.V.)	=3943 cc.
	Measured B.V. (T-1824 P.V. +P^{32} R.C.V.)	=2769 cc.
	Per cent change by the calculated (T-1824) B.V.	= −31 per cent
	Per cent change by the measured (T-1824 +P^{32}) B.V.	= −51 per cent
	Ratio $\frac{\text{B.V. by T-1824} + P^{32}}{\text{B.V. by T-1824}}$	= .70

the estimated normal blood volume; the measured blood volume (T-1824 P.V. + P^{32} R.C.V.) is 51 per cent below the estimated normal value.

In this patient, if one relied on the T-1824 red cell volume determination, no red cell infusions would have been required. In contrast, a deficit of 43 per cent was found by the radiophosphorus red cell measurement, thus indicating the need for a large infusion of red cells to restore the red cell volume to the estimated normal value.

SUMMARY AND CONCLUSIONS

1. Circulating plasma and red cell volumes were investigated with radioactive phosphorus tagged red cells and T-1824 dye in normal dogs, Nembutalized dogs, and splenectomized and non-splenectomized dogs with a standard 20 per cent deep second degree burn. Measurements were made at the sixth hour, 27th hour, and 7.5 days after the burn.

2. The disappearance slopes of T-1824 dye are similar in both the control and six hour post-burn experiments. At the latter time, there was a loss of

28 per cent of the plasma volume. One week after the burn there was a 25 per cent increase in the plasma volume.

3. In 35 normal dogs the average ratio of "radiophosphorus red cell volume" to "T-1824 red cell volume" was 0.98. Nembutal anesthesia did not cause significant fluctuation in this ratio. This would indicate that in *normal dogs* the dye volume—hematocrit formula correctly estimates the red cell volume.

4. In 20 burned dogs the ratio $\frac{\text{R.C.V. by } P^{32}}{\text{R.C.V. by T-1824}}$ was 0.73 six hours after the burn. This ratio almost returned to the pre-burn value by the twenty-seventh hour post-burn and was at the control value one week following the burn. Eight splenectomized dogs responded similarly.

5. The discrepancy in red cell volume estimation by the two methods during the post-burn hemoconcentration phase is probably due to the error of the peripheral centrifuge hematocrit, which is an integral part of the dye calculations. Because the peripheral hematocrit is significantly higher than the actual body hematocrit following a 20 per cent burn in the dog, the dye method overestimated considerably the circulating red cell volume and should not be used for this estimation, nor for the total circulating blood volume during the hemoconcentration phase.

7. The radiophosphorus dilution technic demonstrates an average loss of 11 per cent of the circulating red cell mass at the sixth hour following a standard 20 per cent burn. It is suggested again that whole blood be used in the early post-burn period to replace the entire calculated red cell loss.

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DISCUSSION.—DR. CHAMP LYONS: I should like to add my congratulations for the splendid work that is being done in these quantitative measurements of blood volume deficiency in various types of trauma.

The difficulties of accurate estimates of blood volume are readily apparent. Out of this has emerged one fact of great clinical significance: Adequate replacement of blood volume results in the restoration of urine flow. At the present time we have a clinical method, therefore, of judging the adequacy of blood volume replacement—25 cc. per hour of urine indicates that there has been enough blood volume restoration to overcome the selective renal vaso constriction.

DR. PHILIP B. PRICE: My associates and I have studied experimental burns produced in three ways—by a standard low-temperature burn, similar to that just described, by steam scald for 30 seconds, and by dry Bunsen burner flame.

We find that three types of burn are produced which differ somewhat, both in the local effects on the skin and subcutaneous tissue and also on some of the systemic effects.

The studies of Dr. Herman Pearse reported at this meeting last year suggest that flash burns from exceedingly high temperatures lasting for only a fraction of a second—a sort which seem to be produced by atom bomb explosions—may be still another sort of burn.

The measurements of blood volume make a complex problem. When dye is injected, it diffuses more or less uniformly throughout all the plasma in the circulation; consequently, a sample of plasma taken from an artery or vein is fairly representative of all plasma, and in spite of many difficulties and pitfalls in the technic, comparatively reliable estimates of plasma volume may be obtained.

Unfortunately, in burns, when the heat is 100° or higher, there is a considerable amount of hemolysis, at least during the first few hours, and this has made the measurement of plasma volume extremely difficult. In fact, only recently have we been able to separate dye from hemolized plasma quantitatively so as to give accurate measurements of plasma volume.

When it comes to measurement of blood cell volume, the problem is more difficult, for two reasons. One is that many cells are stagnant, and so they do not get tagged, whether one uses the old fashioned carbon monoxide or whether one uses the newer radioisotopes. This can be obviated in dogs to some extent by removing the spleen ahead of time, as has been done in the work reported today, but even so, there are large numbers of cells which remain stagnant, especially when burns take place. Many of the cutaneous vessels become clotted, and some cells become stagnant.

Another difficulty is that samples of blood which are taken from peripheral vessels do not represent—so far as cell-plasma ratio is concerned—the blood throughout the body, hence any type of blood volume measurement based on hematocrit of samples of

blood taken from an artery or vein (and the artery is better than the vein) will still be quite inaccurate, and I think the work just reported brings that out very clearly.

As far as I am concerned, the only reliable way even to estimate blood volume is to measure the plasma volume and the cell volume independently, and add the two.

DR. EVERETT I. EVANS (in closing): First, Dr. Salzberg and I appreciate more than we can say the comments of Dr. Lyons and Dr. Price. As to the comment of Dr. Lyons regarding urine flow as a measure of the therapy of burn shock, we are inclined—after studying a few hundred patients and following urine flow quite carefully—to more or less come to the same conclusion that he has, namely, that the urine flow is a fairly adequate method of estimating proper replacement of blood. Indeed, I was sorry yesterday, in the discussion on Dr. Stewart's paper, that someone didn't bring out the fact that there is no more remarkable organ in the body to indicate to the surgeon what is going on in central and peripheral blood flow than the kidney. Of all the organs, it seems to be one of the most remarkable, and I don't believe we pay enough attention to urine flow as a measure of peripheral blood flow.

As to Dr. Price's remarks, it appears from his latter remarks that we are in agreement about the importance of measuring blood volume by simultaneous measurement of circulating red cell volume, and the plasma volume, separately.

From a point of view of science, it should be emphasized that these data demonstrate rather conclusively that in normal body states in the dog, one can pretty well estimate red cell volume from the dye hematocrit data. You remember the ratio was .99, practically unity. However, in states of shock it would probably be unwise to rely on red cell volume when the peripheral hematocrit is not a true measure of the body hematocrit.

Mr. President, I wanted to discuss Dr. Stewart's paper yesterday, but there was not sufficient time. We would like to suggest that if, in the future, we are going to learn anything about the proper management of the bleeding ulcer patient—whether he shall be treated by medical management or surgical management—some groups will have to do blood volume studies so that we can have comparative data. It is simply impossible, without such data, to compare one group of patients to another group.

Finally, I should just like to state again, as Dr. Salzberg has stated, that we believe whole blood should be included in the therapy of the severely burned patient. To say this is to indicate that in preparation for civil defense, we must not only think of plasma and plasma requirements, but we must—as Dr. Raydin and Dr. Churchill have indicated many times before this group—say again, "There is no substitute for whole blood"; so in your local communities in the national blood program, we would ask support for those of us who are trying to put this rather simple point across.

AN APPROACH TO THE TREATMENT OF PRESSURE SORES*

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The term pressure sore is preferred to decubitus ulcer because it describes more accurately the cause of these ulcerations. Although several theories have been proposed linking possible neurovascular changes with their production, the opinion is that the predominant factor in etiology is ischemia from prolonged pressure which results in necrosis of the skin and underlying tissues. These terms will be used interchangeably in the text.

The authors wish to acknowledge their gratitude to Dr. Donald Munro, a pioneer interpreter of the bodily changes occurring in paraplegia, to Drs. George P. Denny and Herbert S. Talbot who have directed the Paraplegia Service at Cushing V. A. Hospital and to Drs. Robert Kuhn, José Sârraga, Warren Sisson and M. N. Smith-Petersen, Jr., with whom much of this project has been carried out.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion of the Veterans Administration.

FOUR YEARS AGO before the American Surgical Association two papers were presented on the surgical closure of decubitus ulcers. These were among the pioneer contributions to the modern treatment of these ulcers. Methods and long-term results have been improved since White & Hamm[17] and Gibbon & Freeman[7] presented their material, but the fundamental concept of the merit of surgical attack has remained unchanged. Emphasis in the early reports was on closure of the ulcers with skin flaps; to this has been added radical excision of underlying bony prominences in conjunction with the skin closure. The purpose of this communication is to present a sequel to these papers by reporting experiences at Cushing Veterans Administration Hospital from July 1, 1947, to March 1, 1950, in the care of 152 ulcers on 75 paralyzed patients. These patients represent about one-third of the total number treated on the Paraplegic Service during the period. The remaining two-thirds either had never developed ulcers or had had definitive care previously with a stable repair. Their hospitalization was for treatment of other complications or for training in ambulation.

* Read before the American Surgical Association, Colorado Springs, Colo., April 21, 1950.

Scoville, while at this same Cushing Hospital during the war years, is credited with suggesting the value of definitive surgical closure of decubitus ulcers. However, Davis wrote in 1938[6] that repair of sacral ulcers was possible either by excision and closure or by excision and rotation of a flap. In discussing his results he pointed out the futility of relying on a skin graft for permanent covering. Linear closure of a sacral decubitus ulcer was reported by Lamon and Alexander (1945).[13] Several types of flaps used in the closure of five ulcers were described by White, Hudson and Kennard,[18] who concluded that a rotated flap was the most satisfactory. Closure of five sacral ulcers by developing triangular flaps radiating from the central defect which were partially advanced and partially rotated to meet in the midline was reported by Croce and his associates.[4] Barker, Elkins & Poer[1] describe three different methods in the closure of 70 ulcers—excision and suture, rotation of flaps and free skin grafts. Conway and his associates[3] reported results with closure of 56 decubitus ulcers and concluded that "excision and closure by pedicled flap with free skin graft at a distance" is the most satisfactory method. Blocksma, Kostrubala and Greeley[2] (1949) summarized their experience with 236 decubitus ulcers. They described an important new procedure of radical excision of the ischial tuberosity in conjunction with the skin closure and emphasized the routine reduction of bony prominences, which, if they remain, "reproduce the same mechanical pressure that created the original ulcer."

Pressure sores have occurred with greatest frequency in skin overlying weight-bearing bony prominences. The areas of ulceration most commonly reported during and immediately after the last war were over the sacrum and femoral trochanters. White & Hamm reported eight sacral ulcers out of 14 treated. Gibbon & Freeman reported 65 ulcers, which included 29 sacral, and 26 over the femoral trochanters. Croce[5] (1947) reported 62 sacral and 49 trochanteric ulcers in 130 patients. Forty per cent of the patients reported by Conway had ulcers over the sacrum or trochanters. Following the successful repair of the sacral and trochanteric ulcers a significant increase in the ulcers of the ischial region has been observed. This shift, of course, came after recovery from the acute phase of the injury and was a sequel to prolonged sitting in a wheel chair. Blocksma reported in 1949 that 53 per cent of the operations performed for decubitus ulcers at the Veterans Hospital, Hines, Illinois, were for closure of ischial ulcers. In the series here reported 54 (35 per cent) of the ulcers were in the ischial region, 37 (24 per cent) were over the trochanter and 34 (23 per cent) were over the sacrum. The remaining 27 (18 per cent) were miscellaneous ulcers which will be described.

Fifty-six (75 per cent) of the patients had sustained missile wounds of the spinal cord. The remaining 19 (25 per cent) were the result of military or civilian accident or disease. Thirty-eight (51 per cent) had injury to the lower dorsal cord between D-7 and D-12. Twenty-two (29 per cent) were injured between D-1 and D-6. Two (2.7 per cent) were quadriplegic with

cervical cord injury. Both were from accidental causes. The remaining 13 (17.3 per cent) were lumbar cord or cauda equina injuries. There was no apparent correlation between the level of injury and the nature or distribution of the pressure sores, although an occasional ulceration developed in the scar at the site of injury.

GENERAL CARE

All who have written both about the cause and treatment of pressure sores agree that the maintenance of adequate nutrition and replacement of fluid and protein lost from the open ulcerations is of the utmost importance. The observations of Mulholland and his associates[14] on 35 patients with bedsores offers impressive proof of the significance of general nutrition, both in preventing the development of ulcerations and in the preparation for successful definitive surgical repair. After correcting the below normal plasma protein concentration and the negative nitrogen balance in these patients they reported that the clinical appearance of the ulcers improved and healing progressed. A change in the condition of the ulcers on correcting the deficiency status has been reported by others and was also observed in the patients included in this study. In the latter group of patients the average plasma protein level on admission was 6.7 mg. per 100 cc. with a maximum of 8.0 and a minimum of 5.1. No operations were performed if the level was below 6 mg. per 100 cc. The average red cell count on admission was 4.19 million with a maximum of 5.6 and a minimum of 2.65. The average hemoglobin on admission was 13.02 Gm. with a maximum of 15.8 and a minimum of 10.2. No operations were performed when the red count was below 3.5 and the hemoglobin below 11 Gm. It was difficult to maintain adequate nutrition in several of the patients despite specially prepared appetizing foods high in protein and vitamins. Lack of appetite has resulted from improper care of the pressure sore, but more often a reason was found elsewhere, in urinary tract infection, pain, irregular bowel habits or other complication. Prompt improvement in appetite has followed correction of the underlying cause. Liberal use of blood transfusions proved to be the most reliable means of supplementing a deficient intake by mouth. During all major surgical procedures one or more transfusions have been given routinely, regardless of the degree of blood loss.

SPASMS

Reflex spasms were present in 30 (40 per cent) of the patients. In 22 (30 per cent) the spasms were massive enough to interfere with the successful surgical closure of the ulcerations. Anterior rhizotomy was performed in these 22 patients and the ulcers were then closed without complication. Several patients were reluctant to accept rhizotomy because they had learned how to initiate the spasms and to use them in ambulation. Only after the failure of one or more attempts at surgical closure of the ulcers or the development of additional ulcers was the rhizotomy accepted. Another reason for reluctance

to accept rhizotomy was fear of disrupting established automatic bladder function. Munro[15] has reported that by stimulating the anterior spinal roots during operation and observing the changes in the bladder cystometrically, it is possible to select which roots should be cut and which left uncut. This method of differential anterior rhizotomy was used in these patients and bladder reflexes were unaltered.

LOCAL CARE

The local treatment of pressure sores has changed continuously during the period of this study. A variety of medications, topical applications, and technics have been tried. The present routine established on very simple fundamental principles is aimed at the prompt debriding of the ulcers and rapid preparation for definitive surgery. Considerable variation in the size and character of pressure ulcers has been observed. Sacral ulcerations are usually large and flat, with minimal undermining of skin. There are usually fragments of necrotic fascia or ligament still attached deeply in the ulcer. These must be removed as the ulcer is prepared. Trochanteric or ischial ulcers often have a small surface opening, but beneath is a large cavity into which the bony prominence projects. This cavity is lined with a shiny grayish membrane and may contain sloughing bits of fascia, or infected bone. Profuse drainage and even surrounding cellulitis may be present. With good general and local care, drainage decreases, the size of the cavity diminishes, and the appearance of the wound improves.

Cultures of the pus in these cavities have shown a variety of organisms. *Staphylococcus aureus* has been the predominant organism, but the following have also been frequently found: hemolytic streptococcus, *E. coli, Bacillus pyocyaneus,* diphtheroids, etc. Neither local nor systemic antibiotics or sulfonamides have proved beneficial in the preparation of the ulcers for surgery unless invasive infection has had to be controlled. As a prophylactic measure, penicillin or streptomycin have been given for 24 hours preoperatively and for five to six days postoperatively.

The following routine is currently in use. The patient is kept on complete bed rest and is not permitted to lie on the ulcerated areas. A two hour turning routine is maintained for his remaining unaffected skin areas. Treatment of the local area consists, first, in adequate surgical debridement in the operating room, if necessary, followed by multiple wet dressings. Sponges saturated with full strength Dakin's solution are applied to the raw surface or packed in the cavity and covered by oiled silk to prevent evaporation. This method has produced rapid improvement in the condition of the pressure ulcers. Initially, thrice-daily dressings are performed, then reduced to twice-daily and, as the area heals, to once-daily. The period of time during which Dakin's sponges are used varies. If there are signs of surrounding skin irritation, a layer of gauze impregnated with boric ointment affords adequate protection to the

edges of the wound. In the majority of cases, no irritation whatsover has been encountered with the use of Dakin's solution.

A change to half-strength Dakin's solution is made when there is a clean granulating wound. Later 2 per cent boric acid solution is used to saturate the sponges. Each dressing is preceded by cleansing the ulcer with Phisoderm, hydrogen peroxide or soap and water. This routine requires intelligent co-operation from the nursing staff which must carry out many of the dressing procedures.

Firm healthy granulations, minimal drainage and absence of necrotic tissue in the ulcer are the indications for operation. These local criteria have proved the most accurate of any in determining the proper time for repairing the ulcerations. The general condition of the patient usually improves with the wound and is also an important factor in deciding when to operate.

Definitive surgery with a clean granulating wound can be done safely. If the ulcer is large, with a sufficiently even surface, a temporary skin graft dressing of the open wound has been found preferable. The patient's general nutrition can be more easily maintained when the area is successfully closed with a skin graft. A short period of activity in a wheel chair is allowed before the definitive plastice procedure is undertaken.

The proximity of the common areas of pressure sores to the anus has led some authors to recommend the use of Sulfasuxidine prior to operation. In this series of patients the bowel was emptied thoroughly the day before operation by an enema and the operative area sealed from the anus. The three instances of fecal contamination which occurred resulted from incomplete emptying of the bowel following the enema. Resumption of regular bowel evacuation is started five or six days after operation. The colon has been kept quiet during that interval by the administration of codeine sulphate.

Whether or not the patient has been voiding satisfactorily, he is customarily put on tidal drainage just before operation and this is maintained at least until he can be reasonably active in bed, usually at least six days, and always until he needs no longer be kept on his abdomen. The care of the bladder is then resumed from where it stood just before operation. Those who were voiding well previously almost invariably resume after this interlude.

SACRAL ULCERS

Thirty-four patients with sacral ulcers had surgical closure. Eighteen of these were recurrent or had persisted despite earlier treatment. An average of two operative attempts had been made to heal each of these. The maximum was seven. Sixteen had had no previous treatment. Seven ulcers were superficial, with enough soft tissue remaining over the bone to justify a skin graft (Fig. 1). These grafts have not been replaced, but small ulcers have developed from imprudent weight bearing, and flap repairs may eventually prove necessary. Ten ulcers extended to deep fascia and periosteum, but were small

FIG. 1.—Sacral and trochanteric pressure sores in a patient recovering from the effects of compression on the spinal cord. Stable sacral closure achieved with split skin graft only. Trochanteric ulcer excised radically and linear closure done without excision of bone. Patient now able to walk with canes.

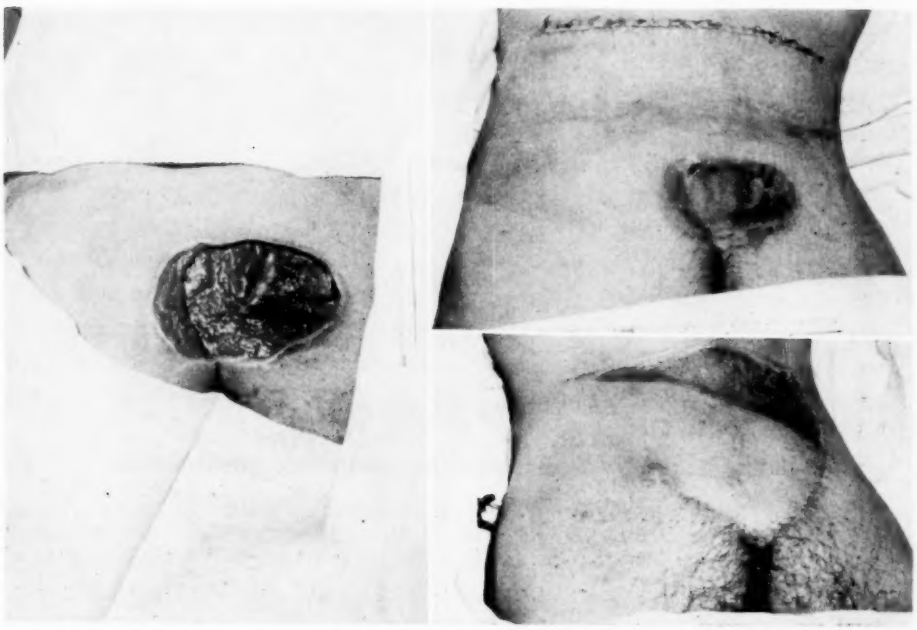


FIG. 2.—Sacral pressure sore healed by primary free skin graft. Final repair done with a delayed flap shifted from the lumbar region. Skin graft used to close donor area of flap. Posterior iliac spines excised.

enough to permit linear closure by mobilizing the adjacent skin. Twelve required closure by a flap from the buttock lateral to the sacrum or from the lumbar region. All flaps transferred from the lumbar region were delayed. If the condition of the raw surface was good at the first delaying procedure it was closed with a skin graft which was discarded when the flap was transferred.

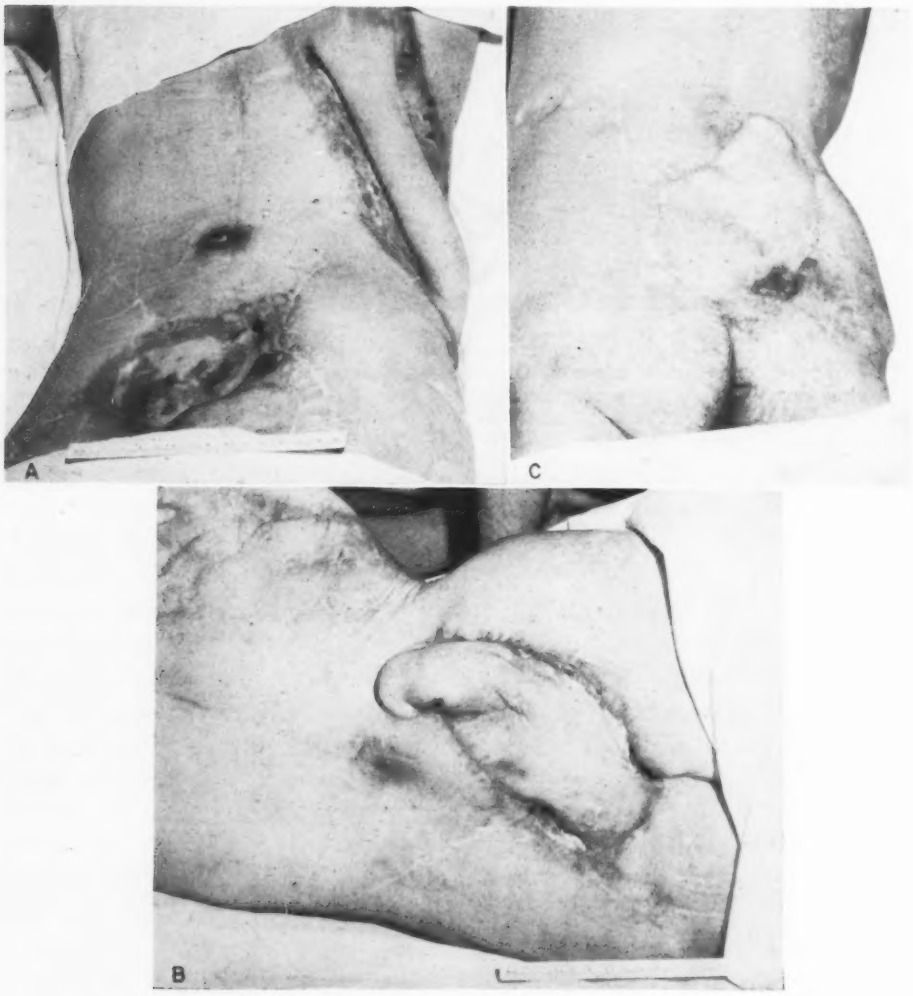


FIG. 3.—Recurrent sacral pressure sore repaired by a delayed tubed flap from the back and flank. Surgical scars radiating from the sacral defect prevented the use of a flap from lumbar region or buttocks. Donor area of flap repaired with a split skin graft.

In each case the donor area of the flap was covered with a skin graft (Fig. 2). Surgical scars radiating from the margins of one sacral ulcer with scarring over the lumbar spine after rhizotomy necessitated the transfer of a flap from the back in multiple stages in one patient (Fig. 3).

The outer table of the sacrum was excised in four cases, three of which required closure with a flap. Removal of the outer table has proved the most effective way to debride the wound of all necrotic fascia and ligament attached to the uneven surface of the sacrum. The resulting healthy cancellous bone provides an excellent bed for skin closure. Prominent posterior iliac spines have been amputated at the time of the definitive closure. If a flap from the lumbar region is elevated, they are usually exposed in the wound. Otherwise, minimal dissection from the margins of the excised ulcer is necessary to expose and excise them.

Five complications of surgical repair of sacral ulcers have been observed. Postoperative bleeding occurred in two cases, neither of which had had excision of bone. In one case there was temporary serous drainage from the wound. In two cases the wound edges separated and healing was delayed.

TROCHANTERIC ULCERS

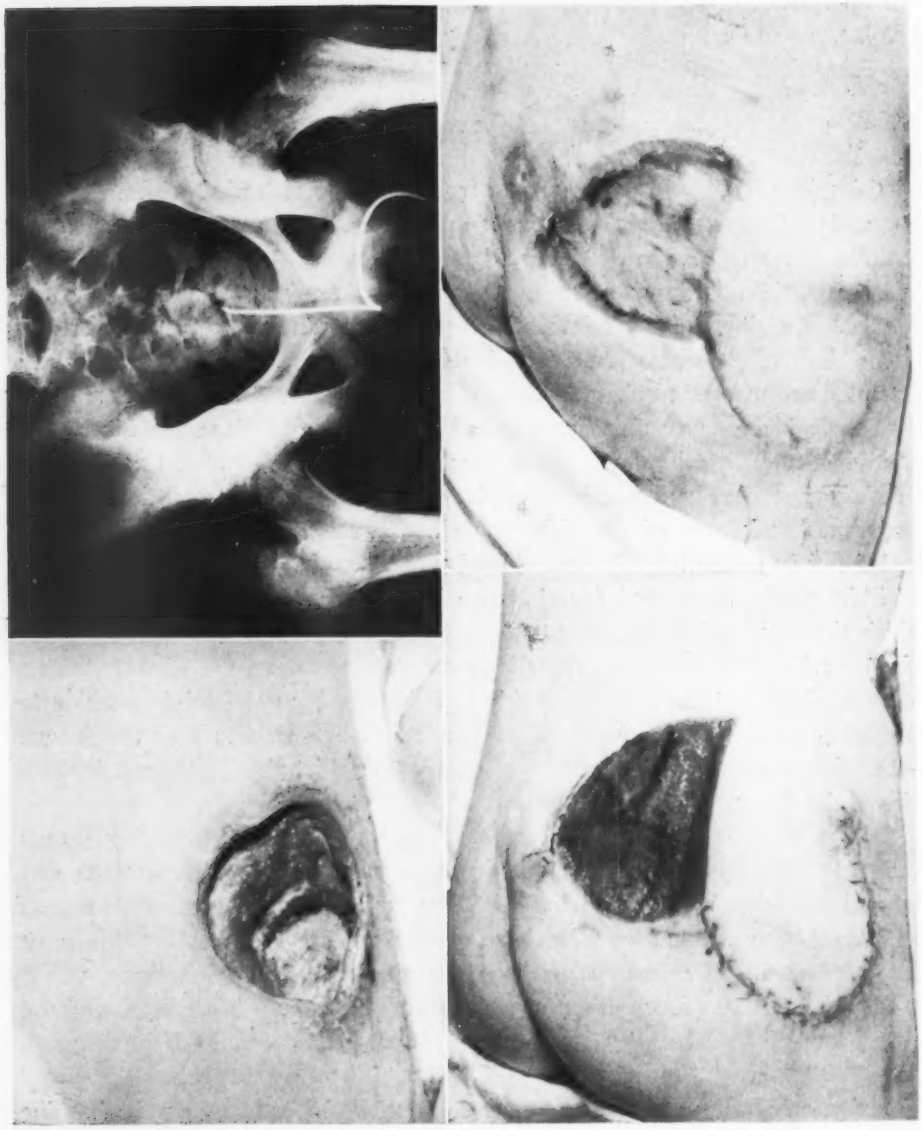
Of 37 trochanteric pressure sores treated, six have healed without operation and 31 have required one or more operations. In 12 of the 31 an average of three operations were done before there was a stable closure. The maximum was seven, the minimum two. Nineteen required only a single operation for closure. Excision of the trochanter and partial decortication of the upper end of the shaft of the femur was done in ten operations because a large cavity extended around the trochanter and neck of the femur. Seven of the ten had previously had one or more unsuccessful operations to close the ulcer. By removing the projecting bone which interfered with collapse of the soft tissues, a definitive stable repair of all ten has been accomplished. A potential cause of recurrent breakdown of the skin was simultaneously eliminated. The skin healed firmly to the healthy cancellous bone exposed by the excision of bone.

Skin grafts were used for closure of six superficial ulcerations beneath which there was adequate subcutaneous tissue over the bone. Linear closure without relaxing incision was done for 14 ulcerations (Fig. 1). Closure with a flap was done in ten cases. A double pedicle flap from the thigh anterior to the defect was used when the defect was parallel to the shaft of the femur. Otherwise, a rotated local flap was used. A split thickness skin graft for closure of the donor sites of the flaps was used routinely (Fig. 4).

There have been eight complications. Delayed healing, following serous drainage from the wound, occurred in three instances. One hematoma was drained and one wound became infected, but each has now healed. One wound dehiscence occurred and there has been one serious recurrence. One skin graft was lost because of reflex spasms, but succeeded following rhizotomy.

There have been four patients with a pyarthrosis of the hip joint associated with a large infected cavity surrounding the upper end of the femur and an ulcer in the skin posterior to the trochanter. Three of these had developed extensive calcification in the soft tissues about the hip and upper thigh. The

FIG. 4. — Trochanteric pressure sore treated by excision of the ulcer, amputation of the femoral trochanter and closure with a direct rotated flap. Skin grafting of donor area of flap ten days later.



calcification resembled myositis ossificans and limited motion of the joint. Attempts at radical excision of the calcified areas and mobilization of the joint were unsuccessful. Infection persisted and sacrifice of the upper shaft, head and neck of the femur was necessary. A large cavity resulted which could not be collapsed by conservative means because of unyielding scar and the rigid projecting wing of the ilium. Amputation was considered but discarded because, despite the unstable hip joint, the patients reported greater stability in sitting with the thigh to lean against. Closure of the cavity was accomplished

FIG. 5.—Example of destruction of hip joint, the result of an extensive trochanteric pressure sore and unsuccessful arthroplasty. Residual cavity closed by further shortening of femoral shaft, amputation of anterior wing of ilium, and transferring the muscle mass from the outer surface of the ilium between the end of the femur and the acetabulum. (Operation performed by Dr. C. R. Rowe)

by excising the wing of the ilium and transferring the muscle tissue from its outer surface to the space between the end of the shaft of the femur and the acetabulum. The fourth patient developed pyarthrosis as a surgical complication of radical excision of an ulcer posterior to the trochanter. Prompt removal of the upper femur and wing of the ilium with collapse of the cavity has been followed by complete healing (Fig. 5).

ISCHIAL ULCERS

Fifty-nine ischial ulcers have been treated surgically. In 45, radical excision of the ischial tuberosity, pubic and ischial rami was done in conjunction

with the skin closure. Although excision of bony prominences had been generally carried out in the presence of the not infrequent hyperoplastic changes in bone evident by roentgen ray, the radical excision of bone as a therapeutic and prophylactic measure was not performed routinely until after 1947, when the method was described by Greeley and his associates[11] (Fig. 6). This has been a most significant contribution. There have been no recurrences in our patients since this method has been adopted, and longer periods of sitting have been possible. Four patients who had a unilateral excision of bone have developed a new sore or abrasion of the skin on the opposite side. This evidence of additional burden on the unoperated side has necessitated a second procedure duplicating that on the first side (Fig. 7). Bilateral single stage radical excision of bone has been done in seven patients, even in the absence of significant skin changes on one side. As both a therapeutic and prophylactic procedure, this method has proved valuable in securing a permanently stable repair (Fig. 8).

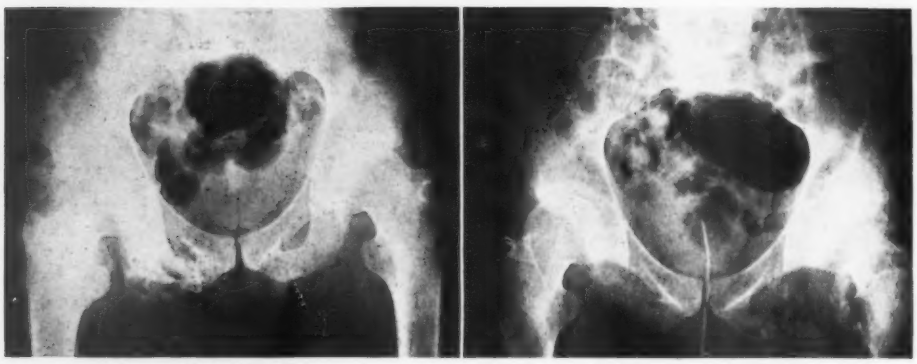


FIG. 6.—Osteitis of right ischial tuberosity associated with ischial pressure sore. Treated by bilateral radical excision of the tuberosities and ischial and pubic rami, in conjunction with excision of the ulcer on the right. Primary closure of the skin was carried out.

Skin closure has been carried out in several days. Of the 59 ulcers treated surgically 32 had minimal skin destruction and have had a simple linear closure. Twenty-five of these had a radical excision of underlying bone at the same time. One or more attempts at closure had been made in 13 of the five ulcers. Five of them were observed to recur because of failure to excise the underlying bone. When this was done, each was closed successfully.

Twenty-seven ulcers of the total of 59 required the use of a flap shifted from the posterior surface of the upper thigh because of considerable loss of skin at the ulcer site (Fig. 9). The donor area of the flap was large enough in 22 to require a skin graft. An average of three earlier attempts at closure had been made in 17 of these. The maximum was eight.

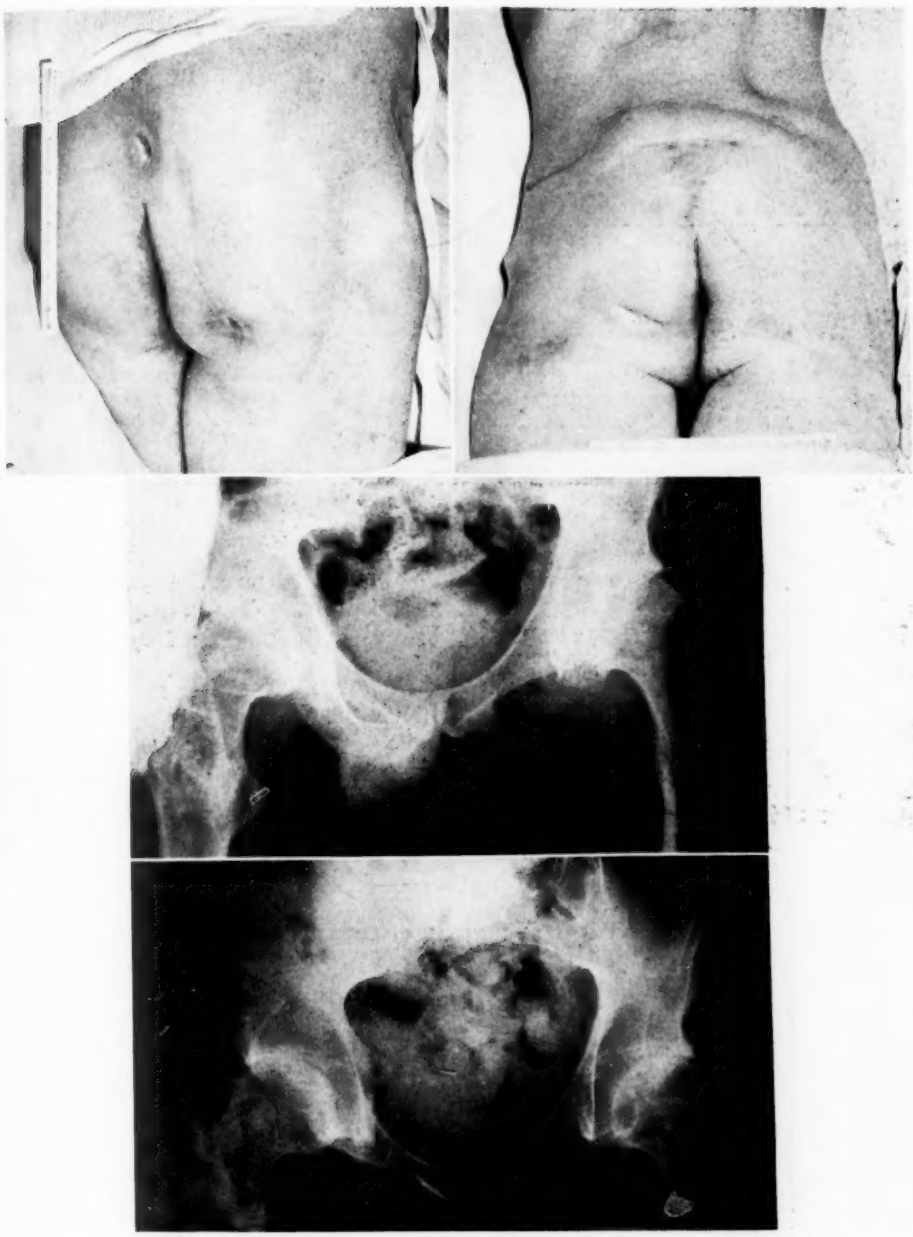


FIG. 7.—Ischial pressure sore on the right treated successfully by radical excision of ischial tuberosity and ramus. Pubic ramus partially excised. Skin over the left ischial tuberosity, intact at the first operation, developed a new sore necessitating a second procedure duplicating that on the right side.

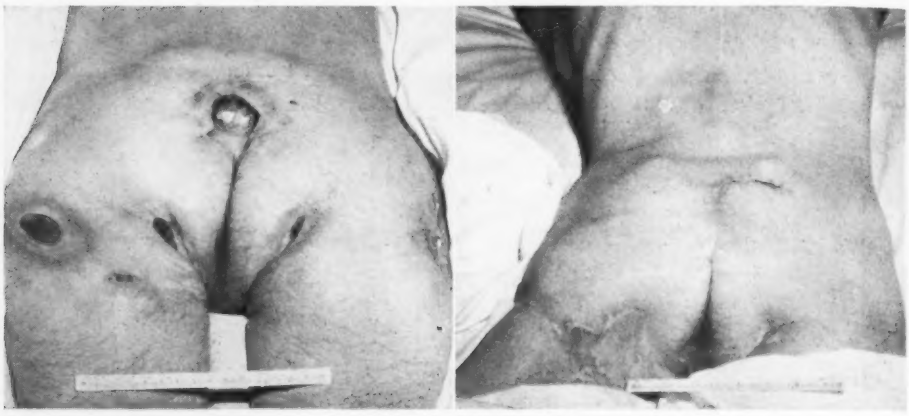


FIG. 8.—Multiple pressure sores of buttock, sacral and ischial regions. Sacral ulcer excised and closed with a rotated flap. Ischial ulcers including ischial tuberosities and pubic and ischial rami excised. Linear closure done on the right, flap closure on the left. Buttock ulcer excised and closed.

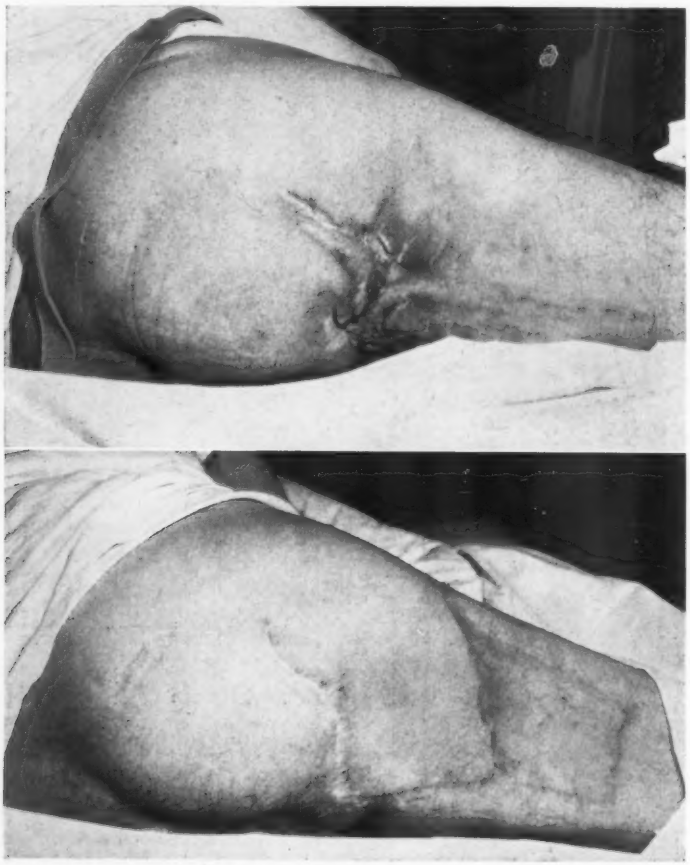


FIG. 9.—Old (W. W. I) ischial pressure sore repaired with delayed flap shifted from upper thigh. Thigh closed with skin graft.

There has been no recurrence in the 45 ulcers in which a radical excision of the ischial tuberosity and rami has been done with the closure. In nine there has been a follow-up of one year. One irresponsible patient with a bilateral radical ischiectomy reported in a follow-up that he has sat for 12 hours at a time without damaging the skin of the buttocks. Examination showed no instability of the scars. The 14 ulcers treated successfully before the radical procedure was a routine have not required re-operation but precautions against prolonged sitting have been necessary to avoid recurrence.

The complications have been hematoma 11, infection five, serous drainage four, wound separation four and partial necrosis of a flap one. Delayed healing occurred in the four instances of wound separation. Most of these complications occurred in the 14 operations done before 1948, when radical excision of ischial tuberosity and rami was adopted as the routine procedure. Four wound hematomata and three instances of fecal contamination have complicated the other 45 operations. Each hematoma was evacuated promptly, the wound re-sutured and primary healing resulted. No hematoma has occurred, since routine drainage of the cavity through a stab wound has been done. The three wound infections were adequately drained and good healing resulted. The rarity of serious complications in recent operations may be attributed to the complete collapse of soft tissue into the cavity, possible because no rigid bony projection interferes. One unforeseen complication occurred in a patient with an extreme lordosis. Because of the forward tilt of the pelvis the symphysis pubis became a weight bearing point in the sitting position and the perineal skin over it became ulcerated. The value of the radical procedure lies in the wider distribution of weight over the buttocks and upper thighs without bony prominences to produce ischemia of the overlying skin.

MISCELLANEOUS ULCERS

The malleolus has been the site of pressure sores in three cases, each of which has been closed with a skin graft. In one of these, the graft has not been stable and may require repair by a flap.

The heel, which is frequently ulcerated in patients who lie on their backs, has not been a serious problem. Only seven have required surgical care. In two, a skin graft has sufficed to give a good closure. Five, in three of which two previous attempts failed, had successful repairs following radical excision of the posterior projecting part of the os calcis, and either linear closure[3] or closure with flaps from either side.[2]

Two ulcerations over the anterior-superior spine have been treated by radical excision of the underlying bony prominence and linear closure. Two others have had skin grafts. The former method is preferable.

One ulcer on the costal margin was successfully repaired with a local flap after three unsuccessful attempts to close it with a skin graft.

One patient who had been careless in the use of braces and shoes had widespread lower leg ulcers exposing both tibial crests. The bony cortex was

removed and skin was grafted successfully on the granulating bone. This patient had ulcers on the dorsum of both feet, also repaired with skin grafts (Fig. 10). Two ulcers on the dorsum of the feet from deep burns were closed with skin grafts. All of these areas have remained healed.

COMMENT

The treatment of pressure sores has been successful because greater attention is paid to the general nutrition of the patient, because surgical closure of

FIG. 10.—Extensive pressure sores of both lower legs treated by decortication of tibia and repair with split thickness skin grafts to the granulating bone and the dorsum of the feet.

the ulcers has become an established procedure, and because improved methods of carrying out surgical repairs have produced results which decrease the likelihood of recurrence or other complications. Rehabilitation of the paralyzed patient within the fixed limits of the extent of the damage to the spinal cord need no longer be hindered by persistent, recurrent or potential ulcerations. These can now be healed permanently by surgical procedures.

Two simple principles have been observed in the surgical repair of pressure sores. They are, to provide a movable healthy pad of skin and subcutaneous tissue over the ulcer site, and, to eliminate all possible underlying bony

prominences which act as focal points of pressure. This study has shown that fewer immediate complications and later recurrences occur when these principles are followed. In 76 per cent of the operations reported herein there was primary healing of the wound. Satisfactory healing was obtained in over 90 per cent.

Various types of skin closure have been described in the literature. From this study it is concluded that a local flap shifted or rotated into the defect from an adjacent non-weight bearing area is preferable for ulcers with significant skin loss. Linear closure is usually adequate for smaller ulcers. If possible, the closure should be planned so that scars will not overlie bony prominences. A relaxed closure permits collapse of the skin into the defect left by the excision and reduces the likelihood of wound separation. Flaps should be mobilized with as few new scars as possible to insure the availability of additional skin should a future repair become necessary. Injudicious incisions, for example, in advancing multiple radial flaps about a sacral ulceration, have interfered with the use of local tissue in subsequent repairs and have necessitated multiple stage transfer of a remote flap.

A free skin graft is useful as a temporary dressing in large flat ulcers to stop the loss of tissue fluids, but in most cases it should be replaced with a flap. A graft can seldom be used for preliminary closure of ulcers with a large underlying cavity. The donor areas of most flaps cannot be closed without a skin graft. Results with delay of the grafting procedure for seven to ten days are better than when it is done at the primary repair.

The radical excision of all possible bony prominences has been an important advance. This has been stimulated by the increasing incidence of ischial ulcers as a consequence of prolonged sitting. The ischial tuberosity, ischial and pubic rami are now excised in all cases of ischial ulcer. There have been no recurrences in patients who have had this type of procedure, and it is now being used promptly as a prophylactic measure if any minor skin abrasion or ulceration develops. Similarly, good results have been obtained when the same principle is applied to the repair of ulcers over the femoral trochanter, the anterior and posterior iliac spines, the os calcis, and occasionally the sacrum.

Most pressure sores are preventable lesions, but to avoid them requires prompt (within the first 24–48 hours) and constant attention both to the local and the general care of the patient. Poor condition of the patient is reflected in impaired vitality of the skin, so that moisture, lack of cleanliness, uneven bedding, rigid casts, or hard mattresses may precipitate the development of an ulceration. Regular shifting of position at least every two hours will relieve the weight on skin overlying the bony prominences. The Stryker frame has proved a valuable aid in the care of patients who cannot move themselves in bed either because of pain or because of high paralysis. It is also valuable if the nursing personnel is untrained or if help is insufficient. On

the Stryker frame the patient can be turned frequently by one person without disturbing his position. Prolonged care on a Stryker frame is undesirable. Once the patient no longer has pain on turning and as soon as he can move himself with minimal help he should be returned to a bed with a soft mattress, preferably of sponge rubber.

Complications have been few. Most frequent has been bleeding, despite careful hemostasis. No significant difference has been observed between ligation of all vessels with fine cotton (120) and electrocoagulation. No delay in healing has followed prompt recognition and evacuation of the hematoma. If not evacuated early the hematoma has caused delay in healing. All wounds with extensive dissection or excision of bone are now drained through a stab wound. Neither hematoma nor infection has occurred in a drained wound.

Infection has not been a troublesome complication despite the fact that most repairs have been done in the presence of an open wound. This is attributed to thorough preoperative preparation of the patient and the wound, to adequate excision of all damaged soft tissue, to partial or complete excision of bony prominences which allows collapse of the adjacent soft tissues, and to closure of the skin without tension, using a flap if necessary.

SUMMARY

Experiences with 152 ulcers in 75 paralyzed patients at Cushing Veterans Administration Hospital have been reviewed and the general and local care discussed. Radical excision of all possibly bony prominences is emphasized and the methods of skin closure described.

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DISCUSSION.—DR. JOHN H. GIBBON, JR.: I was very pleased to hear this report and to note the change in the type of pressure sores which has occurred since the end of the war. Now there are more ischial decubitus ulcers, due to sitting in wheel chairs, whereas during the war sacral decubitus ulcers were more frequent, occurring in patients lying in bed or on stretchers for long periods of time.

The emphasis on the various technical points was interesting. The necessity for excising bone from infected ischial tuberosities is important. One of the important principles in the treatment of decubitus ulcers is the use of local, healthy skin, full thickness, with adequate fat under it. This obviates the risk of recurrent pressure sores, which are prone to occur with the use of free, split thickness, skin grafts.

I am glad to see from recent reports on the surgical treatment of these ulcers that the old shibboleth of trophic nerves has been discarded. In looking up this subject we were interested in finding that many of the older authors did not support the theory of trophic nerves. Despite the complete lack of innervation of the skin, it heals perfectly well, provided that the nutrition is adequate, as Dr. Cannon has indicated.

Finally, I think that one of the most interesting problems in this connection is the question of how long normal, healthy skin, in individuals in an adequate state of nutrition, can withstand complete ischemia. I believe the answer to this question is important to the Army Medical Corps, and to my knowledge it has never been adequately worked out. The Army rule used to be that patients must be turned every three to four hours, and, as Dr. Cannon has said, it is better if they are turned over every two hours. That makes a difficult nursing problem, of course, and many ingenious gadgets have been devised to change the pressure over particular points, so that no area of the skin is exposed to complete ischemia for more than a couple of hours at the most.

The toleration to complete ischemia of highly differentiated nerve tissue such as the brain is in the order of three to five minutes; of less differentiated nerve tissue, such as the spinal cord, 15 to 20 minutes. The peripheral nerves can tolerate considerably longer periods of ischemia. The work of Sir Thomas Lewis in applying a tourniquet to the arm and studying the paralysis brought about in the peripheral nerves of the forearm and hand produced a great deal of interesting information. The period of toleration to complete ischemia in non-nervous tissue is very much longer. It is a very difficult problem to work out in the skin. We have been trying to do so in the past year, but we are still unable to produce conclusive results. I still believe that we

can get a base line in normal, healthy patients by determining the duration of ischemia which will produce blistering. We have been attempting to do that in normal human volunteers by the use of various pressure devices, and so far it appears that periods of ischemia for as long as six hours will not cause blistering of the skin, but we are not yet ready to give any actual figures on this subject.

I think Dr. Cannon should be congratulated on the excellent results which he has reported today.

DR. BRADFORD CANNON: I wish to thank Dr. Gibbon, and to call attention to the excellent discussion of this whole problem of ischemia which was presented in his paper four years ago. At that time he recommended discarding use of the term, "decubitus ulcers," for which reason, in selecting a title for this paper, we chose the term, "pressure sore."

The Striker frame—one of the "gadgets" which Dr. Gibbon has mentioned as a means of alternating pressure and relieving the nursing problem in the care of these patients—has proved very valuable. This frame allows the patients to be turned from face to back by one person. It can be done quite frequently, and we have found it very beneficial in the early care of these patients. In the long-term care, however, it is undesirable, because the patients themselves should begin to be more active in bed as they recover from the initial injury.

THE EFFECT OF POTASSIUM DEFICIENCY ON INTESTINAL MOTILITY AND GASTRIC SECRETION*

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THE EFFECTS produced by a loss of body potassium have been studied in a variety of clinical conditions such as diarrhea, intestinal obstruction, Cushing's syndrome and diabetic acidosis. Potassium deficiency has been produced experimentally by feeding a low potassium diet or by injecting desoxycorticosterone. It was shown that potassium deficiency may lead to muscle weakness and, in dogs, to eventual paralysis. In addition to this skeletal muscle change, pathologic lesions in cardiac muscle occur which are associated with characteristic electrocardiographic changes. In man and animals given desoxycorticosterone, the water exchange is increased.

In order to investigate certain aspects of potassium deficiency, it was decided to study the effects on organs containing smooth muscle and the effect on gastric secretion. In addition, the effects due to loss of digestive juices has been studied in dogs and in several cases with gastro-intestinal dysfunction in man.

To produce potassium deficiency experimentally, animals were fed a low potassium diet (0.01 per cent potassium). In *rats* the tone and movements of the whole digestive tract decreased progressively as the deficiency continued (Fig. 1B, 2B, 3A). In an average of two months, this resulted in severe distension which eventually was the cause of death. The hypotonic intestine was usually filled with large amounts of digestive-secretions, even before symptoms became severe. In many animals in the severe stage of deficiency, large amounts of gas accumulated, so that the condition resembled that of paralytic ileus. These signs rapidly disappeared upon the administration of potassium. The bladder of deficient animals was also atonic and was usually found filled with urine (Fig. 1B).

In potassium deficient adult *dogs*, little change in motility of the digestive tract occurred, although there was a reduction in the strength and rate of rhythmic contractions. In these dogs, water exchange was increased early in the deficiency.

Other studies have been carried out in dogs with gastric-pouches without loss of gastric juice. In potassium deficiency produced by a low potassium diet, the dogs showed an increase in volume of gastric secretion which paralleled the increase in water exchange (Fig. 4). Muscle weakness and eventual

* Read before the American Surgical Association, Colorado Springs, Colo., April 21, 1950.

paralysis developed in these animals and was relieved by the administration of potassium.

In other dogs with gastric pouches which were fed a normal diet of meat, the secretion by the gastric pouch was discarded. Potassium deficiency resulted and the water exchange and volume of gastric secretions increased markedly (Fig. 5). Loss of body potassium due to loss of gastric juice has also been observed by other investigators clinically and in rats.

These studies have shown that simple potassium deficiency in rats greatly reduces motility in the smooth muscle organs of the gastro-intestinal tract and bladder. Because of the accumulation of fluid and gas, there is either an in-

A B

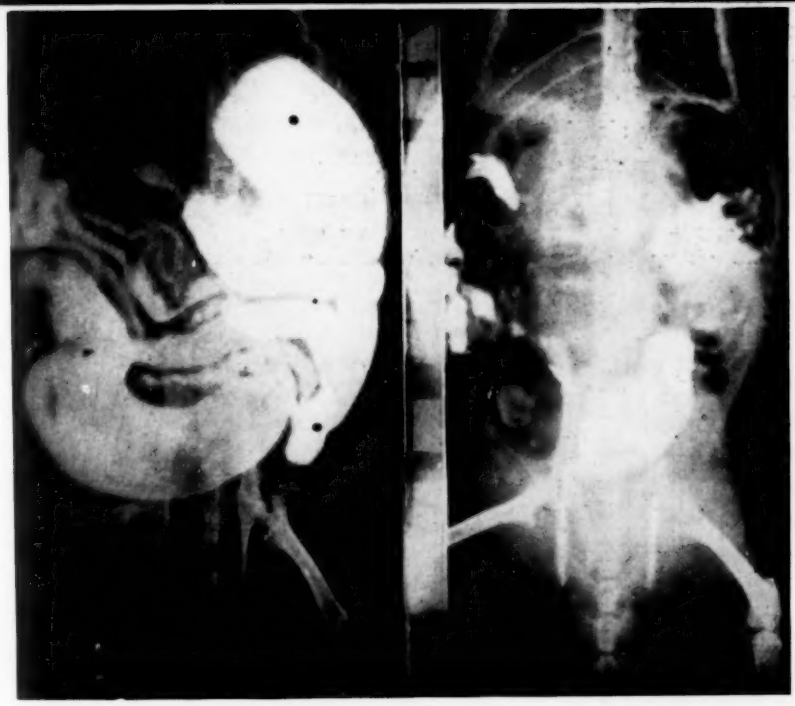
FIG. 1.— (A) Gastro-intestinal tract of normal rat. (B) Hypotonic, distended tract of rat in severe potassium deficiency. Fluid and gas accumulated throughout.

FIG. 2.—Roentgen-ray of same rat. (A) Normal—showing that at five hours much barium was excreted, and the remainder was mainly in cecum and colon, with traces in small bowel. (B) Severe potassium deficiency—14 hours after barium. Barium was in stasis for many hours in the hypotonic, distended stomach and small bowel. No barium was excreted for 48 hours. (C) Recovery on a normal diet five days. Five hour roentgenogram shows the marked improvement in tone, movements and transport. Transport was about two hours slower than normal. Complete recovery was obtained later.

FIG. 3.—Roentgen ray on same rat. (A) Very severe potassium deficiency. Twenty-four hours after a first barium administration, a second dose of barium was given. This roentgenogram taken one-half hour after a second barium feeding shows the marked distention and hypomotility of the whole tract. Complete retention of first meal, mainly in ileum and cecum, occurred. There was practically no evacuation of second barium from stomach in one-half hour or even in four hours. (B) This shows the rapid stimulatory effect of potassium on gastro-intestinal motility and transport of contents. Two meq. of potassium were injected subcutaneously four hours after second meal. This roentgenogram, taken 20 hours later, shows that most of the two barium doses was excreted along with much fluid and gas. No feces had been excreted for a total of three and a half days prior to this.

FIG. 2

A B C

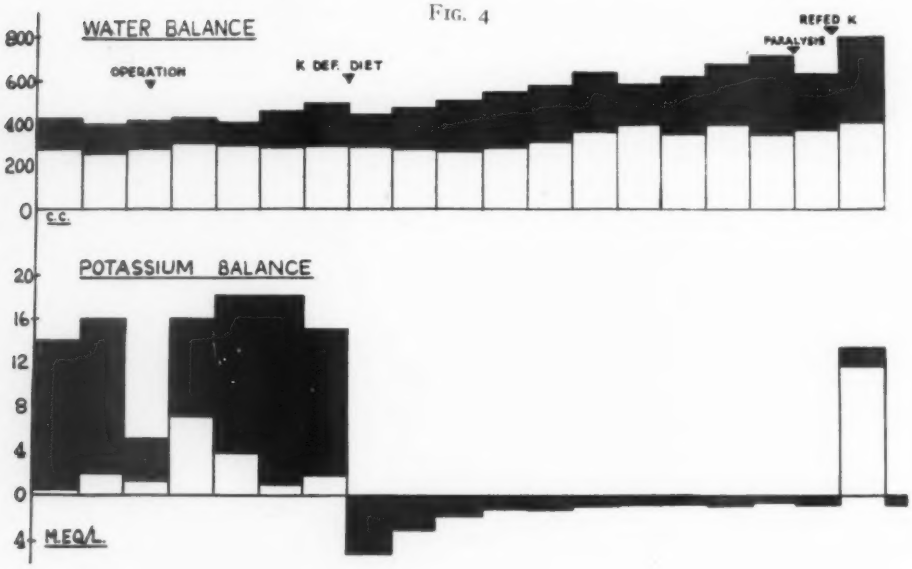


A B

FIG. 3

(Legends on opposite page)

FIG. 4



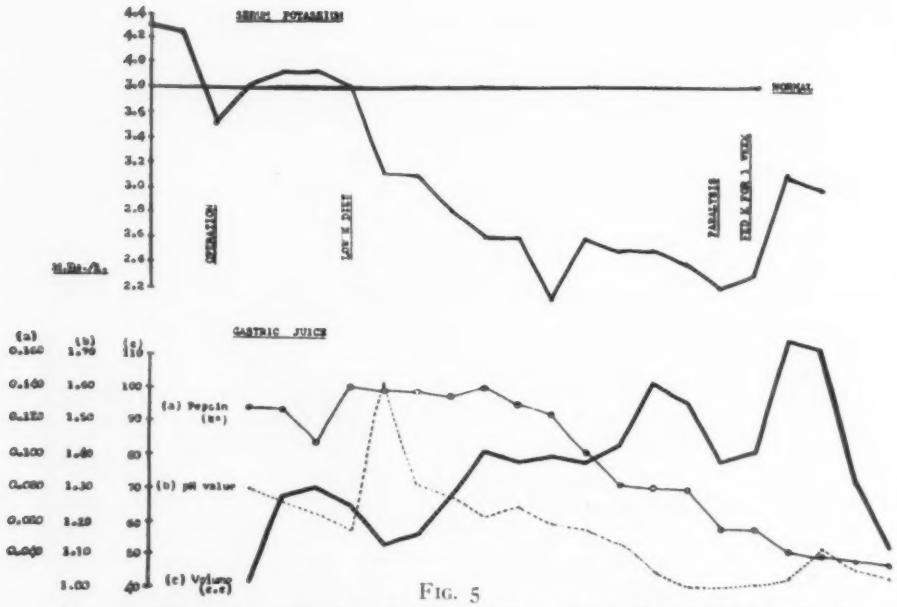


FIG. 5

FIG. 4.—*Water and Potassium Balance in Dog with a Gastric Pouch.* Intake in each case is shown by the upper limit of the black block above the base line. The output is measured downward from the upper limit of the black block and is indicated by the lower margin of the block. Therefore positive balance is shown by a clear area above the baseline, a negative balance by a black block below. Note the steady increase in water exchange with potassium deficiency and the negative potassium balance postoperatively for several days. When potassium was fed, there was an effort to conserve potassium as shown by the positive balance.

FIG. 5.—This chart shows that as the serum potassium decreases from feeding a low potassium diet, the volume of gastric juice increases. Note also that the gastric pouch dog pepsin tends to decrease in concentration and the juice becomes more acidic.

creased secretion of digestive juices and/or a decreased absorption. In potassium deficient dogs, the water exchange and volume of gastric secretions is increased.

A clinical illustration is provided by a patient who had a perforation of a diverticulum of the cecum. A cecostomy was performed by the surgeon, Dr. Harry Ballon, and continuous gastric suction was used postoperatively. The cecostomy did not function for three weeks. The patient lost up to eight litres of gastric secretion each day. Parenteral glucose, physiologic saline, and plasma were given intravenously. At the end of this time, although the patient was not paralyzed, the peripheral reflexes were absent. The serum potassium was 9 mg. per 100 cc., the serum chlorides were 290 mg. per 106 cc. and the carbon dioxide combining power was 100 volumes per 100 cc. of serum. Ammonium chloride was administered with little or no improvement. When potassium chloride was administered, the cecostomy began to function and the patient made an uneventful recovery.

So it would seem that when gastric and intestinal secretions are lost from the body, a relatively large amount of potassium is likewise lost, as these fluids contain two to three times as much potassium as an equivalent amount of serum. Two effects may ensue:

1. There may be inhibition of the intestinal musculature aggravating an ileus already established from some other cause.

2. There appears to be a stimulus to increase the volume of gastric secretion. The stomach continues to secrete potassium, and because of the increased volume of secretion, the potassium deficiency develops. Hydration and electrolyte balance can only be restored if potassium is administered.

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DISCUSSION.—DR. ROBERT ELMAN: I would like to congratulate the speaker, Dr. Webster, and his co-workers on a very important contribution to our knowledge of this complicated and very interesting subject of potassium deficiency.

We have all seen patients with gastric retention, in which there has seemed to be insufficient organic evidence of obstruction. We have been accustomed to say that part of the mechanism is due to an atony of the stomach. It may well be that a deficit in potassium plays a significant part in the pathogenesis.

Although we have studied the plasma level of potassium in many of these cases, a correlation with clinical manifestations has seemed to be rather inconstant. Nevertheless, we have recently added potassium chloride to the saline solution in the treat-

ment of dehydration from pyloric obstruction, and have been impressed on a clinical basis with the rapidity with which the gastric retention disappears. At the Barnes Hospital, on each division, we have supplied sterile solutions* of 20 per cent potassium chloride, 5 cc. of which, when added to a liter of glucose, saline or amino acid solution, will furnish 1 Gm. of potassium chloride. As much as 4 Gm. can be added.

The great danger in giving potassium chloride occurs in the patient with anuria. I think it is relatively safe as long as the patient is putting out urine. However, it must be given most cautiously, especially in patients with renal insufficiency and azotemia, even though there is a good urinary output. If one attempts to give more than 4 Gm. of potassium chloride in a liter, even when given slowly, there is always the danger of pain and phlebitis.

Dr. Everett I. Evans: I apologize for getting up twice the same morning, but feel this is an extremely important subject. Dr. Bigger and I have had an opportunity to study a really large number of patients with potassium deficiency, in most of whom it wasn't suspected until real attention was paid to the problem. It is much more common, we feel, than we ever thought, and I must say, also, that we are not too convinced of the value of blood plasma-potassium levels as indications of the extent of the deficiency.

I hate to disagree with my friend, Bob Elman, but I am a little concerned—and Dr. Bigger and I both feel this way about it—about having on hand strong potassium solutions ready for the house officer to give. We have heard of one patient who received this concentrated solution. I think the patient recovered, but extremely high blood levels were reached. We prefer to order potassium chloride as 2 Gm. added to each liter normal saline, and not have the strong solution around, where the danger of giving the concentrated solution is always present.

Finally, I would like to add a note to Dr. Webster's important contribution; it is this: We studied this problem in almost exactly the same manner as you did, Dr. Webster, but only studied the dogs up to about 30 days, and did not find this peculiar inertia of the bowel. Apparently we would have to go on to longer periods of potassium exhaustion before we reached these important findings referred to by Dr. Webster. The patient seems to develop and show signs of potassium deficiency much sooner than the experimental animal.

Dr. Francis D. Moore: The question of species differences is really an awfully important one, and I would be interested to know if the diet reported really produced a *monovalent* K deficiency without a deficiency of other essential dietary constituents.

I also think we should emphasize again the difference between body *cell* K depletion, which is very common in surgical patients, and *extracellular* deficiency, which is very rare. Any patient who has been losing extrarenal body fluids for two or three days intake has a body cell K depletion. This is hard to demonstrate. The only way we have been able to demonstrate it is by measuring the total body potassium by K-42 dilution. This is in sharp contrast to plasma K depletion, which is produced very rapidly, especially in the presence of acidosis or alkalosis, and demonstrated very simply by a plasma potassium determination.

As far as the physiologic effects are concerned, the two are very nicely differentiated. A low plasma K produces a disorder in neuromuscular induction most notably shown by electrocardiographic changes. Cell K loss produces a disorder of muscular contraction as seen in the gut and in peripheral paralysis. These rats are interesting because they had both. They had both body cell K depletion and a low plasma K, and when we see that combination in patients, it is also a difficult problem to treat.

* Each bottle contains a maximum of 40 cc. so that at most 8 Gm. of KCl can be added.

As to using K solutions on the wards, I think we should all talk in the same terms, namely, milliequivalents per liter. We have used a K solution now for several years, containing 40 milliequivalents of K per liter as KCl. We have used it carefully, as has been emphasized by one of the previous discussers. We have steered clear of patients who were anuric, but if used carefully and slowly we do not feel it is dangerous. As several have emphasized, the clinical benefits derived in patients with peritonitis—draining ileostomies, and so on—seem wholly out of proportion to the laboratory evidences of improvement.

DR. D. R. WEBSTER (in closing): I would just like to thank the discussers. I would like to add that it is rather difficult to give the potassium too fast, as the patient complains of the pain when it is given intravenously.

In considering the rat and the dog, probably the intestinal tract of the rat resembles human beings more than the dog does. It is an omniverous animal, and the cecum is larger proportionately in the rat than in the dog.

BOOK REVIEW

A COMPANION IN SURGICAL STUDIES. Ian Aird, Ch.M., F.R.C.S., Baltimore, Williams and Wilkins Company, 1949. Price $15.00. 1060 pages.

One's attention is attracted to this book immediately, not only because of its unusual title but also because it is done entirely by a single author and is a surgical text without illustrations. It is written by Mr. Ian Aird, who is Professor of Surgery in the University of London and Director of the Surgical Unit at the Postgraduate Medical School of London. Obviously written for the advanced student in surgery, it serves its purpose well. It is by no means a rearrangement of a number of pre-existing texts, but rather represents an epitome of the published experience of others, drawn chiefly from particular articles, to which the author has added his own experience and judgment. One cannot but be impressed by the magnitude of the performance. The entire field of surgery, with the exception of fractures, orthopedics and gynecology, is covered; and the area of reference, though not exhaustive, is for the most part adequate. This extensive information has been annealed into a useful and compact form by Aird's obvious surgical sanity, his considerable clinical experience, and his intimate knowledge of many of the disciplines basic to surgery.

The value of single authorship in such a text is well illustrated by its balance, its consistency, and its cohesiveness. The defections of single authorship also are seen. Certain subjects are handled better than others. It would be difficult to find a more lucid and concise consideration of diseases of the arteries, of intestinal obstruction, or of peptic ulcer. On the other hand, in the chapter on neoplasms of the brain and in that on lesions of the breast, adherence to an old and rigid pathologic classification has made biologic correlations seen elsewhere in the book impossible.

On the whole, however, this volume represents a publication of great distinction—one that is destined to occupy a place on many of the book shelves of surgeons on this side of the Atlantic and certainly one in which both the author and the publishers can be justly proud.

NATHAN A. WOMACK, M.D.

SURGICAL TREATMENT OF CALCIFICATION OF THE PANCREAS*

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THE DEPOSITION of insoluble calcium salts in the ducts and acini of the pancreas appears to be a not uncommon consequence of recurrent pancreatitis.[1, 2] The direct cause of this chemical abnormality is not known. While the appearance of calcification on roentgen ray films is a visible evidence of pancreatitis, it in no way alters the course of the disease, nor should the treatment be different. It is a mistake to consider calcification of the pancreas out of its proper context, that is, an incident in the course of a disease entity. The occurrence of this incident does not change the pattern of pain, its rhythm, the progressive digestive symptoms due to external pancreatic deficiency, or the eventual outlook.

On the basis of Archibald's concept that the diversion of bile into the pancreatic ducts is brought about through a common biliary-pancreatic passageway by spasm of the sphincter of Oddi,[3] 73 patients with proved pancreatitis were treated by section of the sphincter of Oddi.[4-6] Among these were four with roentgenographic evidence of calcification of the gland. Herewith are abstracts of the clinical course of these patients:

Case 1.—F. J. (Bellevue Hospital, 4485–48) was a 50-year-old male with a history for 13 years of attacks of severe upper mid-abdominal pain, radiating to the epigastrium and left upper quadrant, lasting 2 hours to 2 days and occurring 2 to 3 times a month. These attacks usually followed a large meal and were most severe if food were taken after a prolonged alcoholic spree. There was no history of diarrhea. Roentgenograms of the abdomen revealed widespread calcification of the pancreas (Fig. 1); roentgen ray films of the gallbladder showed normal visualization of dye; the duodenum showed deformity, suggestive of duodenal ulcer. The glucose tolerance curve was normal. A secretin test showed moderate diminution of pancreatic function (total volume 105 cc.; total amylase 297 units). Since the symptoms were similar to those of non-calcified recurrent acute pancreatitis, and since he had adequate external and internal pancreatic function, it was decided to treat him as a case of recurrent acute pancreatitis.

At operation, February 9, 1948, only a few adhesions were present at the fundus and ampulla of the thin-walled gallbladder. The pancreas was markedly enlarged throughout, very hard, and had a cobblestone-like surface. The head of the pancreas pushed the duodenum forward and distorted it. A thin scar on the anterior duodenal wall was suggestive of a healed duodenal ulcer. A cholangiogram showed an enlarged common bile duct with distortion due to pressure from the pancreas, but the pancreatic duct was not visualized (Fig. 2). The gallbladder was removed and the common duct opened. Due to difficulty in passing the sphincterotome through the papilla, the duodenum was opened and the instrument passed through under vision. The blade was then opened,

* Read before the American Surgical Association, Colorado Springs, Colo., April 21, 1950. Aided by a grant from the National Institute of Health, United States Public Health Service, Grant RG 807.

retracted and the sphincter sectioned. Two weeks after operation, cholangiographic studies again failed to visualize the pancreatic duct. Reflux studies[7] proved the presence of a common passageway. Kymographic studies showed only a slight response to acid, indicating possibly incomplete section of the sphincter, but the response to morphine showed excellent functional destruction. The patient was last seen March 27, 1950, more than 2 years after operation. Although he has continued to drink, he has had no

FIG. 1 FIG. 2

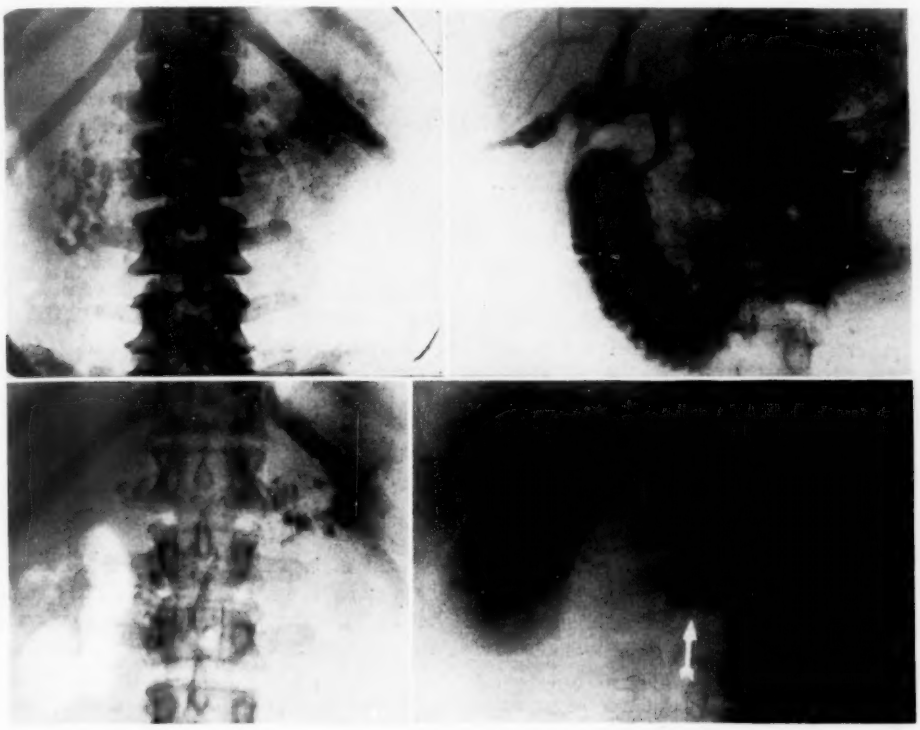

FIG. 3 FIG. 4

FIG. 1.—(Case 1) Preoperative roentgenogram showing widespread calcification of the pancreas.

FIG. 2.—(Case 1) Operative cholangiogram showing enlargement of the biliary tract with angulation and distortion of the common duct in its passage behind the pancreas. The pancreatic duct was not visualized.

FIG. 3.—(Case 1) Roentgenogram taken two years after sphincterotomy showed no evident change in the degree of calcification of the pancreas.

FIG. 4.—(Case 2) Preoperative examination showing a normally functioning gallbladder with calcification of the head of the pancreas (arrow). The rubber tube is draining the pancreatic fistula.

symptoms since operation, and has gained about 10 lbs. in weight. Roentgen ray films of the abdomen taken January 19, 1950, showed the pancreatic calcification unchanged (Fig. 3).

Case 2.—J. G. (Bellevue Hospital, 906–48) was a 36-year-old male admitted to the psychiatric division of Bellevue Hospital on February 24, 1948, in a semi-stuporous condition due apparently to insulin hypoglycemia. He had a history of attacks of severe

epigastric pain radiating to the back for 11 years. In 1940, cholecystostomy and drainage of a pancreatic cyst for obstructive jaundice due to the cyst, was performed at another hospital. After 2 years the attacks of severe epigastric pain recurred and he became a morphine addict. In 1945, also at another hospital, following studies which indicated marked diminution of pancreatic function, an attempt at a pancreatectomy was abandoned and a splenectomy and drainage of a pancreatic cyst was carried out. He developed a persistent pancreatic fistula. Attacks of epigastric pain persisted. At this time, the patient developed diabetes for which he required 55 units of insulin daily. He continued to have attacks of severe pain associated with paralytic ileus on occasions.

Studies at Bellevue Hospital revealed a severe diabetes (glucose tolerance curve: 173,235,333,308 mg. per 100 cc. sugar at ½ hour intervals). Injection of the pancreatic fistula visualized part of the pancreatic duct and showed free communication with the duodenum. Roentgenogram of the stomach and duodenum revealed a normal stomach with some obstruction of the duodenum. Secretin tests could not be done due to failure to pass a duodenal tube. Roentgen ray studies revealed a normal functioning gallbladder as well as calcification in the head of the pancreas (Fig. 4). He required frequent injections of Demerol for pain and to alleviate morphine withdrawal symptoms.

At operation on April 5, 1948, the gallbladder was found to be surrounded by dense adhesions. The pancreatic fistula communicated with the body of the pancreas which was thickened and fibrosed throughout. The head was hard, irregular and enlarged. Many large veins coursed around and over the gastrohepatic omentum, duodenum and pancreas. The common duct was located only after a cholangiogram was done through the cystic duct following removal of the gallbladder. The common duct was wide above and tortuous in its passage behind the head of the pancreas. The pancreatic duct was not visualized. The common duct was opened and a fine probe passed into the duodenum. The duodenum was opened and the sphincter of Oddi was cut over the probe. The pancreatic duct was seen to be emptying into the common bile duct 4 mm. above the papilla. A fine catheter was passed into the duodenum through the bile duct and brought out at the lateral angle of the wound. The pancreatic fistula was excised in its whole length from the skin to its connection with the main pancreatic duct. The opening which remained in the pancreatic duct was anastomosed to the overlying stomach over a small rubber tube. Cholangiograms taken 2 weeks after operation showed ready entrance of the contrast medium into the duodenum. Following injection of morphine the duodenal musculature was shown to be intact.

The patient has been free of pain since his discharge 2 years ago, and is completely cured of his narcotic addiction. The pancreatic fistula has remained closed. He has gained 12 lbs. in weight and his diabetes is controlled by 25 units of insulin daily. A roentgenogram taken on March 31, 1950, showed no obvious change in the calcification of the pancreas (Fig. 5).

Case 3.—D. R. W. (Beth Israel Hospital, Newark, N. J.—operation with Dr. A. Abrams) was a 40-year-old white male with a 12-year history of attacks of severe epigastric pain radiating to the back and to both upper quadrants, occasionally accompanied by vomiting. The attacks lasted from 2 hours to 2 days and at first occurred about every 6 months, but in the last few years the severe attacks occurred every few weeks and he had pain after eating almost every day. Ten years ago a diagnosis of perforated ulcer was made but no operation was done. Between 1940-1944 he was admitted to 4 different military hospitals. Many roentgenograms showed a normal gallbladder and normal stomach and duodenum. He was finally discharged from the army February 11, 1944, because of incapacitating pain. No diagnosis was made. Examination by a civilian physician in 1947 revealed calcification of the pancreas (Fig. 6). A cholecystostomy was performed but by request of the patient the pancreas was not removed. He had no pain as long as the cholecystostomy was functioning. As soon as the drainage tube was removed the attacks of pain recurred. A secretin test done on

April 12, 1948, revealed marked impairment of the pancreas (total volume 120 cc.; total amylase 65 units). At operation on April 16, 1948, the pancreas was found to be large and very hard with an irregular knobby surface. The gallbladder was removed. An operative cholangiogram showed dilatation and distortion of the biliary tract with marked narrowing in the retro-duodenal part. The pancreatic duct was visualized

FIG. 5 FIG. 6

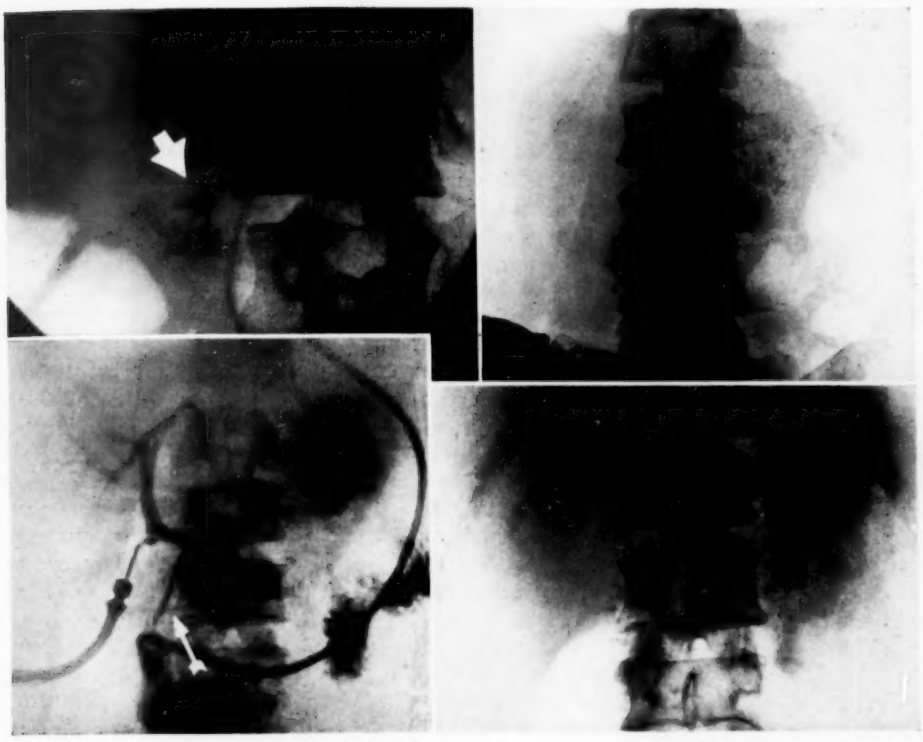

FIG. 7 FIG. 8

FIG. 5.—(Case 2) Two years after sphincterotomy (arrow) the degree of calcification of the head of the pancreas has remained unchanged.

FIG. 6.—Widespread calcification of the pancreas first noted 11 years after the onset of severe attacks of pancreatitis.

FIG. 7.—(Case 3) Operative cholangiogram showed distortion of the common duct with marked narrowing in the retro-duodenal part due to pressure of the enlarged pancreas. The pancreatic duct (arrow) was visualized.

FIG. 8.—(Case 3) Roentgenogram taken 21 months after sphincterotomy showed no change in the degree of calcification of the pancreas.

(Fig. 7). The common duct was about twice its normal size, and very tortuous, owing to its passage behind the enlarged irregular head of the pancreas. The common duct was opened, the sphincterotome passed into the duodenum and sphincterotomy done. The common duct was sutured and a small drain placed down to the line of suture. The drain was removed in 48 hours. In spite of occasional bouts of alcoholism, he has had no pain since operation 2 years ago. However, he requires 6 Gm. of pancreatin daily to prevent bulky diarrhea. He has gained about 15 lbs. in weight. Roentgenogram of the abdomen on January 7, 1950, revealed no change in the degree of calcification (Fig. 8).

Case 4.—P. D. (Bellevue Hospital, 387664–49) was admitted for the first time to the Third Surgical Division on November 24, 1949, complaining of recurrent attacks of epigastric pain of 20 years duration, and loss of 78 lbs. in weight in the past 2 years. The attacks were brought on originally by nervousness or excitement and lasted 1 to 2 days. Since 1937, when he began to drink excessively, the attacks became much more severe, radiated to the back, and lasted 1 to 2 weeks. In spite of a number of operations at various hospitals (cholecystectomy, 1939; repair of a para-esophageal hernia, June, 1949, and exploratory laparotomy, August, 1949), the recurrent attacks increased in severity. In addition, for the past 2 years, pain occurred after every meal. Prior to the last operation in August, 1949, calcification of the head of the pancreas was noted (Fig. 9). A secretin test on November 29, 1949, revealed marked impairment of pancreatic function (total volume, 80 cc.; total bicarbonate, 20 cc. and total amylase 56 units).

At operation, December 1, 1949, hard dense adhesions were found binding the liver, small intestine and transverse colon to the diaphragm. The pancreas was very large, hard and irregular, and had pushed the duodenum upward and to the right. The common duct was found to be thin-walled and narrow. A cholangiogram could not be done due to multiple needle holes produced in the efforts to locate it. A probe was passed into the duodenum and the sphincter sectioned transduodenally. The pancreatic duct, located after the injection of secretin, was found to join the bile duct 6 mm. above the papilla. A probe was passed 4 cm. up the duct without encountering an obstruction. A fine tube was inserted and the pancreatic duct visualized by means of Diodrast (Fig. 10). It was dilated and tortuous but not obstructed. The duodenum was closed and a T-tube inserted in the common duct.

Cholangiographic studies two weeks later, revealed that the T-tube was lying in the common hepatic duct, and that the choledochus lay behind the duodenum and the enlarged head of the pancreas (Fig. 11). The cystic duct and a small remnant of the gallbladder was still present. The dye ran readily into the duodenum. Following the administration of morphine the duodenal wall could be seen to compress the intramural part of the common duct (Fig. 12), proving that the one-way valve action to prevent duodenal reflux was intact. Manometric study showed that the resistance to flow of bile was 120 mm. water.

The T-tube was removed on December 28, 1949, and the patient discharged on January 6, 1950. When last seen on March 28, 1950, he was asymptomatic and had gained 30 lbs. in weight. His appearance and outlook have improved remarkably. He has returned to work and seems to be strikingly rehabilitated. Roentgenogram of the abdomen on March 2, 1950, showed no change in the degree of calcification (Fig. 13).

DISCUSSION

Many procedures heretofore performed for the surgical management of pancreatitis with calcification have been directed not at the disease but at one incidental manifestation. Pancreatectomy has been advocated.[8] This operation is very difficult because of the fixation of the gland and the occasional presence of a surrounding venous dilatation. The poor results in terms of mortality, resultant diabetes, and digestive disturbances overbalance the relief of pain which some patients have exhibited.

Removal of the calcific deposits is not a logical attack on the disease.

Interruption of the autonomic nerve fibers transmitting pain sensation is a successful maneuver for relief of the pain.[2, 9, 10, 11] However, the accompanying diarrhea and fat intolerance, the diabetes, if present, and general nutritional deterioration may progress.[10]

Recurrent attacks of acute pancreatitis may not be accompanied by overt pain or the symptoms may be so vague as soon to be forgotten. The damage with each attack may eventually convert the gland into a fibrosed organ, oocasionally complicated by calcification. It is not surprising therefore, that cases of calcification are reported without any previous history of pain. Such a case noted on our service is outlined:

FIG. 9 FIG. 10

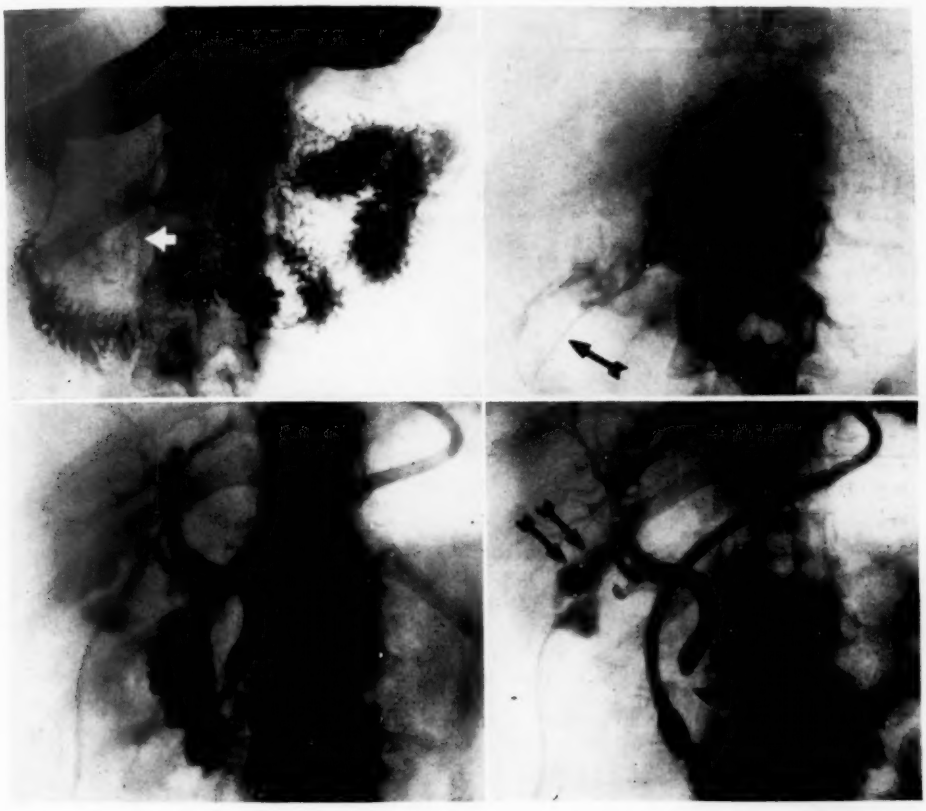

FIG. 11 FIG. 12

FIG. 9.—(Case 4) Preoperative roentgen ray studies showed calcification of the head of the pancreas (arrow) with marked narrowing and distortion of the duodenum.

FIG. 10.—(Case 4) Operative pancreatogram showed the proximal half of the main pancreatic duct to be markedly dilated and tortuous but not obstructed. Visualization was achieved by injecting Diodrast through a fine tube (arrow) inserted into the pancreatic duct.

FIG. 11.—(Case 4) Postoperative cholangiogram showed the T-tube to be lying in the common hepatic duct. The common duct and the cystic duct (left behind at a previous operation) were clearly visualized by the dye which ran readily into the duodenum.

FIG. 12.—(Case 4) Following the administration of morphine, the postoperative cholangiogram showed compression of the intra-mural part of the common duct (arrow), demonstrating that the one-way valve action of the duodenal wall was intact. The cystic duct could be seen to communicate with a very small remnant of the gallbladder (two arrows).

Case 5.—A. M. (Bellevue Hospital, 75767–49) was a 57-year-old man admitted to the 3rd (New York University) Surgical Division on October 8, 1949, with a 2-day history of severe vomiting and diarrhea, following the eating of mushrooms picked in a field. Although the white blood count was 16,250, there were no abdominal signs or symptoms except moderate distention. The vomiting stopped after one day in the hospital. However, a routine serium amylase on October 10, 1949, was 815 mg. per 100 cc. Close examination of the roentgen-ray films of the abdomen showed calcification of the head of the pancreas (Fig. 14). The serum amylase on October 11, 1949, was 1100 mg. per 100 cc. and then gradually decreased. At no time did he complain of abdominal pain or tenderness. A careful history showed that the last attack of vomiting occurred after

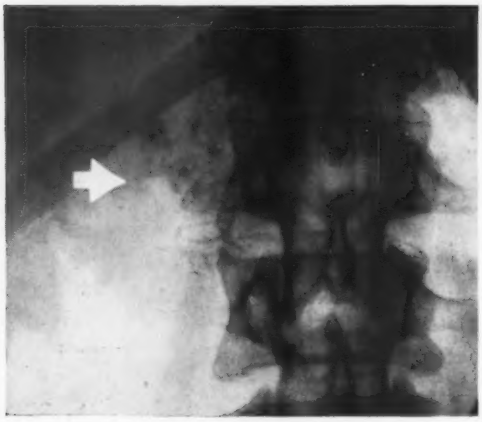

FIG. 13

FIG. 13.—(Case 4) Roentgenogram three months after operation reveals no change in the degree of calcification of the head of the pancreas (arrow).

FIG. 14

FIG. 14.—(Case 5) Calcification of the head of the pancreas (arrow) in a patient with a normally functioning gallbladder (dye concentrated). The only symptoms were occasional attacks of nausea and vomiting.

eating mushrooms fried in olive oil, and that he had had similar attacks of sweating, nausea and vomiting for the past 3 years. Each attack lasted 3 to 4 days. At no time was abdominal pain or tenderness present.

Roentgen ray examination of the gallbladder, stomach and duodenum showed no abnormality except for a small duodenal diverticulum. A secretin test revealed normal function (volume 165 cc. bicarbonate 98 cc. and amylase 1084 units).

Although the patient refused operation, we believe that serious consideration should be given to operative section of the sphincter of Oddi even in the absence of pain. Prevention of further reflux of bile and recurrent episodes of pancreatitis will stop the progress of the disease.

The abolition of pain and the gain in weight following sphincterotomy in the four patients described above proves that the pain in calcification of the pancreas is due to recurrent pancreatitis and not to the presence of calculi.

Although this operative procedure in advanced cases may not improve function already lost, it should prevent further deterioration of the gland.

SUMMARY

Calcification of the pancreas occurs as an occasional incident in the development of chronic pancreatitis. Pain, if present, will be abolished, and recurrent severe attacks of pancreatitis prevented, by section of the sphincter of Oddi. This simple procedure will arrest the progress of the disease, and salvage the residual external and internal pancreatic function.

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DISCUSSION.—DR. LESTER R. DRAGSTEDT: I have been interested in this problem of the pathogenesis of acute pancreatitis or acute pancreatic necrosis for many years.

It is possible to produce the disease experimentally in animals in a great variety of ways, but of all of these experimental methods for producing pancreatitis, the one most likely to occur in human pathology, it has always seemed to me, is the reflux of bile into the pancreatic duct, as postulated by Opie and by Archibald.

I think this recent work of Dr. Mulholland and Dr. Doubilet has provided us with very important evidence confirming the view of Archibald and Opie. They have clearly demonstrated the existence of a common channel in patients with recurrent acute pancreatitis.

Not only do we have that positive evidence with respect to the relation of reflux of bile to the disease, but we also have negative evidence from the very large amount of surgery on the pancreas, both in man and in animals, that has been done in recent years.

One of the prevailing theories of the pathogenesis of pancreatitis proposes that it is due to obstruction to the pancreatic duct. We have obstructed, and ligated the pancreatic duct in dogs many times—over a hundred times—and have never seen acute pancreatic necrosis in animals produced by that method, and I suspect that just as many obstructions to the pancreatic duct in man have been performed in the course of pancreatic surgery without acute pancreatitis developing.

Since this publication of Drs. Mulholland and Doubilet, I have had occasion to use this operation on two patients with recurrent attacks of acute pancreatitis. We did not have the special scissors that these authors have devised, but I simply opened the duodenum, exposed the ampulla, and divided it under direct vision.

In both of these patients the recurrent attacks of pain were entirely relieved. One patient has been observed for about 14 months; the other one has been done just recently, so we have not had a long period of observation, but there has been a change in the clinical picture in the former patient, the first patient, that has been very impressive.

From the standpoint of the experimental studies on this disease, it seems to me that the conclusions of these authors are sound. In all probability, in most—but possibly not all—cases of pancreatitis, there is a reflux of bile into the pancreas, and the favorable results reported by the earlier surgeons from external drainage of the common bile duct, it seems to me, are in harmony with that point of view.

Dr. Ralph F. Bowers: I think we owe a debt of gratitude to Drs. Mulholland and Doubilet for pointing out the fact that something can be done for these distressed patients. They have clearly shown that release of obstruction of the common bile duct at the sphincter of Oddi will relieve these patients of their pain and the recurring attacks.

Diversion of the flow of bile from the ampulla of Vater to a distant nonrelated site in the intestinal tract should also bring about relief of pain and cessation of attacks. Our four cases of pancreatitis, one with calcification, were subjected to choledochojejunostomy en Roux-Y. After severing the common duct and the jejunum, the proximal end of the common duct is anastomosed to the distal jejunal end and then, of course, the intestintal tract is reunited by jejunojejunal anastomosis. As I see it, we employ the same principle as they except a complete shunting of bile is accomplished, which is absolute and hopefully permanent. All four patients have had brilliant recoveries, and we have followed some of them for more than two years.

We agree with them about the role of calcification. We pay no attention to the calcification, but treat the pancreatitis.

I am interested in their new viewpoint—that operation should be employed early in those with calcification, however asymptomatic they may be, in order to prevent subsequent pancreatic dysfunction.

During the last year two cases of calcified pancreas were observed. These patients demonstrated weight loss, weakness, and steatorrhea, but experienced no pain and at no time during the courses of their illness did they have attacks which one could attribute to pancreatitis.

The first man was explored and the pancreas found to be soft except for the stones. A few stones were removed, several bits of pancreatic tissue were submitted to the laboratory for microscopic study, and to our amazement a pathologic diagnosis of adenocarcinoma of the pancreas was made. The involved area did not present the usual sensation of hardness or induration that one feels in the usual pancreatic cancer. A partial pancreatectomy and splenectomy were accomplished. The patient is alive six months postoperatively, but in a terminal state with numerous metastases.

The second patient was operated upon only a few months ago. He is in his late forties and presented the same picture of pancreatic difficulty with loss of weight and weakness, but with no pain whatsoever. When we explored his pancreas we found

that the tissue felt very much like green leather, a different texture than the tissue of the carcinoma case. All studied sections of numerous bits of tissue revealed the condition to be a fibrosing pancreatitis, with a paucity of pancreatic cells and glands. We did not employ choledochojejunostomy in this case, because the patient suffered only from pancreatic deficiency, had not suffered pancreatic attacks, and according to our reasoning, had to all practical purposes undergone physiologic pancreatectomy.

The literature contains very few reported cases of calcification of the pancreas associated with carcinoma. Only two cases had been reported prior to 1938. Dr. Cattell has told me about two other cases, and a third case was published by the Guthrie Clinic. Another case was the one I briefly described.

I do not believe that carcinoma of the pancreas is very commonly seen in association with calcification of the pancreas. I cite these two cases as one in which we did not believe that the shunt operation or sphincterotomy would be beneficial.

DR. ROBERT ELMAN: This work of Dr. Mulholland and Dr. Doubilet is really based upon a number of years of very extensive physiologic and pharmacologic study. Their procedure of cutting the sphincter of Oddi represents a physiologic operation.

I had the opportunity of performing this operation on several patients, with complete success, in the relief of both biliary obstruction and pain. However, I have preferred—as Dr. Dragstedt has—to open the duodenum to do so, which I think has several advantages.

In the first place, one can sometimes detect and visualize other lesions than spasm. In one of my cases there was a definite stricture.

In the second place, one occasionally—as Dr. Bowers mentioned—may pick up an early carcinoma.

In the third place, it seems to me better to do a plastic operation under direct vision with suture of the cut edges rather than to cut the sphincter blindly.

This operation, being simpler and more physiologic, should compete successfully with sympathectomy and, of course, it is somewhat less radical than pancreatectomy.

I would like to congratulate the essayists on a very important therapeutic contribution.

DR. JOHN H. MULHOLLAND: The importance of progressive destructive pancreatitis with calcification and without pain, is illustrated very well by a recent patient of ours, a 59-year-old man who had been treated for 17 years for diabetes. During recent years he had complained of diarrhea and fatty stools, loss of weight, and finally, jaundice. It was the jaundice which brought about his admission to the hospital. Upon admission, the first x-ray film taken disclosed the presence of extensive calcification of his pancreas.

Another patient who had recurrent attacks of so-called "food poisoning" was found during one of his attacks to have a serum amylase level of 1100 mg. per 100 cc., and then also to have calcification of his pancreas.

We believe that in these patients without pain, operation should be seriously considered. Not only will arrest of the progress of pancreatic deterioration be affected but also the pancreas may display its well known property of regeneration. This is possible if active acinar tissue is not imprisoned in fibrous tissue or calcium.

It is also pertinent to point out that spasm of the sphincter of Oddi is a functional derangement which is a manifestation of some other deeper difficulty. In our ignorance, we call it "personality difficulty." Some of these patients are alcoholics, others are unhappy, emotionally frustrated individuals.

The destruction of the function of the sphincter is definitive only in so far as the pancreatitis is concerned. The deeper difficulties persist and may bring about other derangements of the gastro-intestinal tract, such as colitis, and spasm of the pylorus.

Thus, as in duodenal ulcer, the surgeon is doing his best in the face of the failure of more direct measures which are perhaps in the province of the psychiatrist, or due to the lack of ability on the part of the patient to face life's situations.

I would like to mention, too, that the technic of the operation is simple even in the face of extensive varicosities which are formed because of obstruction to the splenic vein or the portal system. The sphincter can be approached through the common duct by the instrument which Dr. Doubilet devised, or it can be approached very simply through a small opening in the duodenum.

DR. JAMES T. PRIESTLEY: I enjoyed the presentation of Dr. Mulholland and Dr. Doubilet as I have their previous contributions to the subject of pancreatitis. It certainly is a subject about which we still have many things to learn.

There are several points that I would like to make regarding pancreatic calcification. In general, every effort should be made to institute satisfactory treatment for recurring pancreatitis before it has advanced to the stage in which there is diffuse calcification throughout the pancreas. As the authors have stressed, calcification of this type represents a late stage of the disease and results from recurring episodes of inflammatory reaction. This often means that function of the pancreas has been largely destroyed and insufficiency of both the internal and external secretory function of the pancreas exists. Under these circumstances, although the patient's pain may be relieved by appropriate procedures, function of the pancreas cannot be significantly restored as a rule, so that the ultimate result leaves considerable to be desired. The point is, of course, that the disease process in the pancreas should be halted before it progresses to such an advanced degree.

The second point I wish to make, which is illustrated by some slides, is that I believe we should distinguish between pancreatic calcification and pancreatic lithiasis. The former term commonly is employed to designate calcification in the parenchyma of the gland and the latter to indicate calcareous material within the pancreatic ducts. Although the former condition is much more commonly seen in association with pancreatitis, nevertheless the latter condition occasionally does occur and it is important to recognize it when it does. If stones develop within the pancreatic ducts, obstruction to the flow of pancreatic juice occurs with resultant damage to the pancreatic parenchyma. Obviously such obstruction may hasten reduction of pancreatic function, if it is not recognized and relieved.

Slides illustrating such a case are presented. In this case calculi were removed from the main pancreatic duct.

DR. OWEN H. WANGENSTEEN: I rise only to relate the observations and thinking of some of my associates on this problem. As Dr. Dragstedt has stated, the reflux of bile up the pancreatic duct has been the favorite thesis since the days of Opie, but there has been not too good clinical substantiation apart from suggestions like those related today by Dr. Doubilet, following up on the work of the late Dr. Archibald of Montreal. I want to remind you too that my associate Dr. N. Logan Leven described the observation of regurgitation of lipiodol into the pancreatic duct during cholangiography several years ago (Proc. Soc. Exper. Biol. & Med., **38**: 808, 1938).

Dr. Carter Howell, a Fellow at the Veterans Hospital in Minneapolis under Drs. Lyle Hay and George Bergh, got the idea that, when cholangiograms were made through a T tube in the common duct, he would see if, in the presence of evidence of a common channel of bile and pancreatic ducts, as indicated by retrojection of the medium into the pancreatic duct, whether the blood amylase was raised: it was. In all patients, in whom Drs. Howell and Bergh observed the pancreatic duct on the cholangiogram (35 patients), there was a very distinct rise of blood amylase, and in the patients, in whom the pancreatic duct was not visualized following the injection of the Diodrast into the T tube, no rise in the blood amylase was observed. These are significant observations.

Dr. Lyle Hay then contrived the idea of diverting the pancreatic juice completely away from the ampulla, rather than slitting the sphincter of Oddi. My own reaction

to Dr. Hay's proposal was to make a long common duct by uniting the distal end of the severed common bile duct to the oral end of a jejunal loop about 25 cm. in length.

Dr. Hay countered with a better idea. In his first patient he divided the pancreatic duct and ligated it, believing the patient had an intact minor pancreatic duct, which subsequent studies of duodenal content proved to be the case. In his next three patients, however, Dr. Hay implanted the severed duct of Wirsung into the duodenum at a lower level. These people have had complete relief of their pain and have not had recurrent attacks of pancreatitis.

I only want to say that I believe these observations of Drs. Howell, Bergh and Hay lend substantial credence to the idea that pancreatitis is, in all likelihood, essentially a regurgitation phenomenon. And by the same token, is it not proper to ask whether pancreatic calculi, too, may not be owing to regurgitation of bile into the pancreatic duct? It is a thesis worth exploring, I believe.

DR. HENRY DOUBILET (closing): I should like to thank the various discussers of this paper very much for the certain points which they raised.

I think the statement that we have tried to approach the problem in its physiologic aspect is most important. It is true that we have applied these physiologic observations clinically, but we have raised a great many other problems, of course, which we cannot answer at this moment.

The operation itself is, one might say, an incidental result of these investigations, because I believe that as we go further on the problem of the physiologic function of the pancreas, we will get more interesting, and possibly very profitable, results in the future.

Certain practical points come up in this treatment. In a patient with a large, hard, fibrosed pancreas, with or without calcification, does cancer exist, or will it form in the future? It is frequently impossible to make a diagnosis, even by biopsy, at the preliminary operation, and we have treated those patients, as far as we could, as cases of chronic pancreatitis, since we could not make a diagnosis in many of our biopsies.

We had one patient who turned out to be a case of carcinoma of the pancreas.

Dr. Bowman, in his book on pancreatitis, mentions the experiences of Whipple, where he had three or four cases which eventually turned out to be carcinoma, although that was not found to be so at a biopsy at a preliminary operation. That is a problem which we have to face.

There is also the difficulty, of course, of occasional isolated stones, as Dr. Priestley mentioned. In a recurrent pathologic process all variations can exist, and it is always possible that a single stone will form in a duct and work its way free and obstruct the main duct of Wirsung. We have to keep our mind open to this possibility.

Generally speaking, the problem of calcification is essentially the problem of chronic pancreatitis, with recurrent attacks of acute pancreatitis.

We have also found—as Dr. Wangensteen stated here—that if you put severe back pressure on the pancreatic duct, it causes an elevation of the serum amylase and, of course, that will occur only if the common passageway is present.

Regarding the observation by Howell and Lillehei, as mentioned, it is undoubtedly true that if you can prevent reflux of bile in the pancreas, you should prevent further attacks in the majority of cases. Whether an operation of completely transplanting the pancreatic duct is better than mere resection of the sphincter, I suppose time will tell.

HEMORRHAGE FROM ESOPHAGEAL VARICES

SURGICAL MANAGEMENT*

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THE SURGICAL TREATMENT of bleeding esophageal varices is unsatisfactory in the majority of cases despite recent interesting and extremely valuable contributions to attempts at decompression of the portal bed by various short-circuiting procedures. The revision of these procedures by Blakemore[1-4] and Whipple[24-26] and their addition to the older measures of splenectomy, omentopexy and esophagoscopic injection of sclerosing solutions into the varices, have raised the hope that a definitive solution to the problem might be at hand. Unfortunately, however, the accumulated experience of both clinicians and surgeons has not fulfilled this hope completely. Technical difficulties and concomitant risk incident to achieving a satisfactory shunt, inability to maintain patency of the venovenous stoma once it has been established, and the inapplicability of establishing a shunt in patients with esophageal varices but with no evidence of increased tension in any of the available portal tributaries, have limited the application of these procedures, and the early enthusiasm as to their ultimate results already seems to be waning. More recently, Phemister and Humphreys have resorted to esophagogastric resection in two cases with encouraging results, and Wangensteen[22] has stressed the erosive action of regurgitated acid chyme as the factor precipitating hemorrhage from established varices, an idea expressed many years before by Kegaries[9] (1933). The production of esophagitis and even esophageal stricture by regurgitated gastric acid chyme has long been emphasized by Vinson, Butt, Olsen and others.[6, 23]

ANATOMIC CONSIDERATIONS

As a preface to subsequent surgical considerations, comment relative to the anatomy involved would appear to be appropriate. Unfortunately, despite the extensive literature upon Banti's disease and cirrhosis of the liver, emphasis has centered preponderantly upon the portal system to the relatively complete neglect of the equally important azygos system. From a morphologic and physiologic standpoint, one is impressed with the similarity between the azygos system and the saphenous system (Fig. 1). The azygos vein corresponds to the greater saphenous vein in such morphologic details as the long, straight, vertical course, the numerous tributaries at all levels and the rather abrupt

* Read before the American Surgical Association, Colorado Springs, Colo., April 21, 1950.

angulation to empty into a major afferent vessel of the right side of the heart. The hemiazygos vein likewise is similar in morphologic detail to the lesser saphenous vein, inasmuch as it, also, runs a straight but shorter course, receives many tributaries, and terminates in the azygos vein after angulating across the ninth thoracic vertebra, similar to the manner in which the lesser saphenous vein terminates in the popliteal vein in the popliteal fossa.

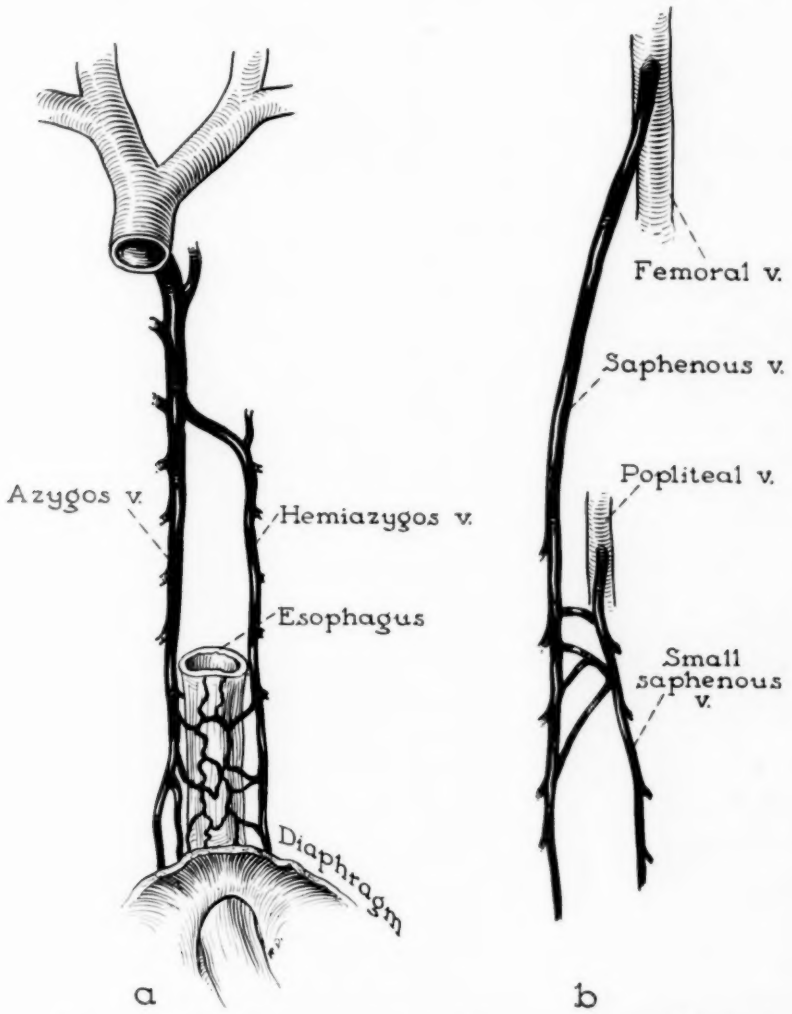

FIG. 1.—Diagramatic representation of the morphologic similarity between the azygos system of veins (a) and the saphenous system of veins (b).

The lower part of the esophagus is cradled between the azygos and hemiazygos veins. Its submucosa is richly supplied with veins which derive only poor support from the loose connective tissue about them. These submucosal veins communicate with longitudinal periesophageal trunks which are tribu-

taries of the azygos system. Communication between portal and caval systems occurs at this level through anastomosis of the esophageal veins with branches of both the coronary vein and the splenic vein (vasa brevia). Any block in the portal system, regardless of its cause, will increase the venous

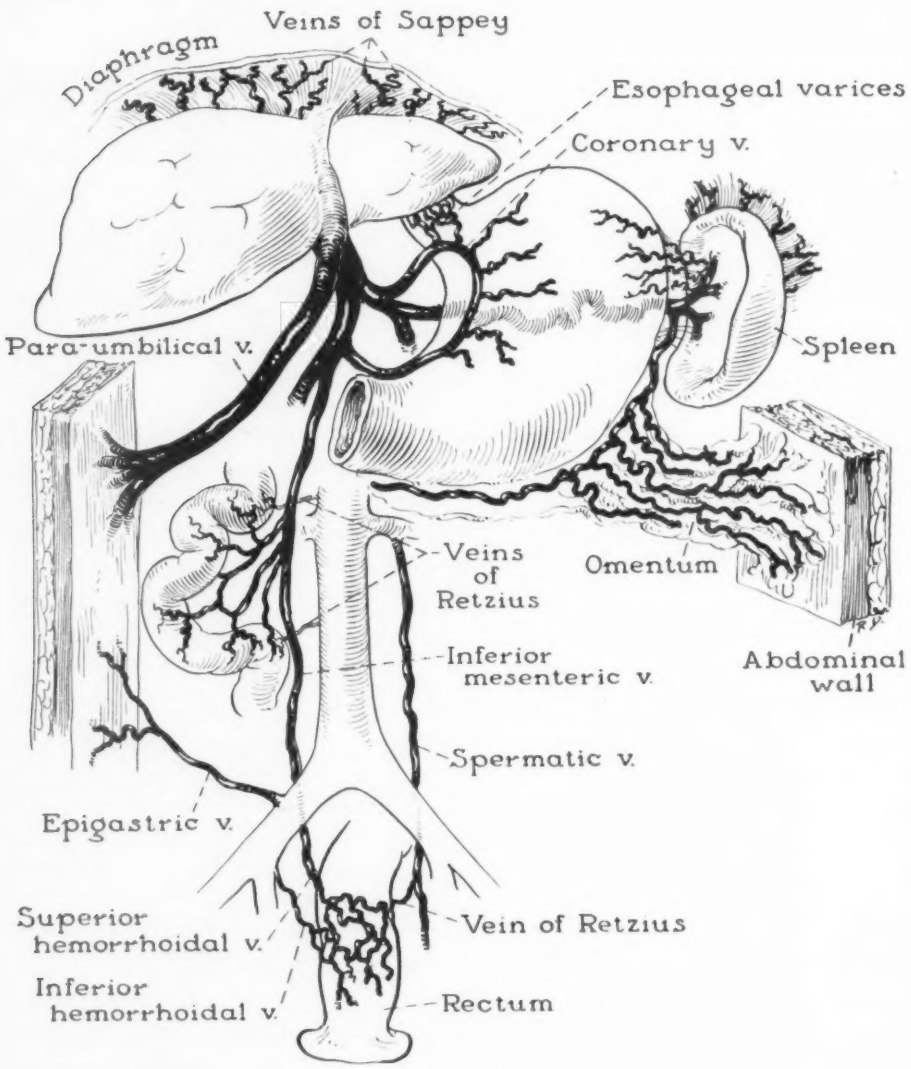

FIG. 2.—Collateral venous channels which may develop in obstruction of the portal system.

pressure distally (Fig. 2). Inability of the muscular and elastic fibers in the walls of the esophageal veins to withstand this pressure may result in varices. In cirrhosis this block is intrahepatic, and in obstruction of the splenic vein or in obstruction of any other tributary of the portal vein the block is extra-

hepatic. In those cases in which portal hypertension cannot be demonstrated in the presence of esophageal varices one cannot help but wonder if in addition to these mechanisms on the portal side of the venous arc, esophageal varices might not also at times have a primary origin on the azygos side. Stasis or passive congestion in the azygos system, coupled with the absence of valves, the poor support afforded the esophageal veins by their loose surrounding stroma, and possibly some inherent structural defect in these veins could produce varices despite normal pressure gradients in the portal system. The possibility exists, in some patients who have been found at operation to have what apparently were a normal spleen, a normal liver, and portal pressures which were within normal ranges, that the esophageal varices may be attributed to abnormalities in the azygos system, when the usual assumption would tend to incriminate abnormalities in the portal system. Experimental and clinical proof for such an hypothesis, however, is lacking at present.

Equally neglected anatomically have been the arterial trunks bringing blood to the lower part of the esophagus (Fig. 3). These trunks take origin from three main sources: (1) ascending branches of the left gastric artery which originate near the cardia, (2) the left inferior phrenic branch of the abdominal aorta and (3) branches directly from the descending aorta. All these vessels run, for the most part, extramurally in a longitudinal direction along the viscus.

Intimately related to the esophagus are the vagus nerves. The right trunk descends behind and the left trunk in front of the organ. Walters and co-workers[21] have shown that complete section of both trunks can be achieved transabdominally in 92 per cent of cases.

SURGICAL CONSIDERATIONS

The surgical management of bleeding esophageal varices has involved three fields of endeavor: (1) reduction of the volume of blood entering the portal vein[7, 10] (splenectomy), (2) removal or destruction of existing varices which are surgically accessible (injection of varices and surgical removal of the lower part of the esophagus and the cardia of the stomach)[12, 15, 20] and (3) protection of the patient as well as possible against the development of new varices and the decompression of existing varices by shifting the circulatory burden to the inferior vena cava or one of its tributaries (portacaval shunts, Talma-Morison operation, and so forth).[2, 11, 17, 26] Attempts to prevent the possibility of mucosal erosion in the region of varices caused by regurgitation of gastric acid chyme has not been suggested, so far as we are aware. In the hope of achieving protection against further hemorrhage, three patients, who may be classified as falling into a combination of the above-named categories, underwent the combined procedures of devascularization of the lower part of the esophagus, splenectomy and bilateral vagotomy with encouraging results to date. In two of these cases gastro-enterostomy was added as a supple-

mentary procedure. These cases are reported in a subsequent section of the paper.

Devascularization in the strict sense of the term would, of course, be incompatible with a viable esophagus. The term is used here to denote the stripping away of any large varicosed periesophageal veins and the ligation and excision of the arterial trunks which ramify outside the muscularis of the viscus, the procedure being extended to include a significant portion of the veins over the cardia of the stomach. The periesophageal veins may be huge in size, plexiform in arrangements, devoid of function as a source of "run-off" for the submucosal plexus, and probably greatly contributory to the stasis and

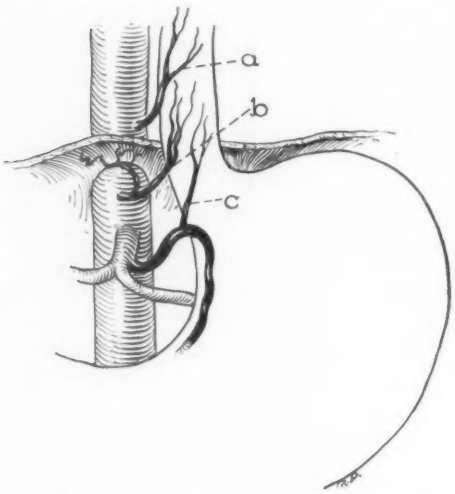

FIG. 3.—The arterial supply of the lower part of the esophagus. (a) Aortic branches; (b) the left inferior phrenic artery; and (c) the ascending branches of the left gastric artery.

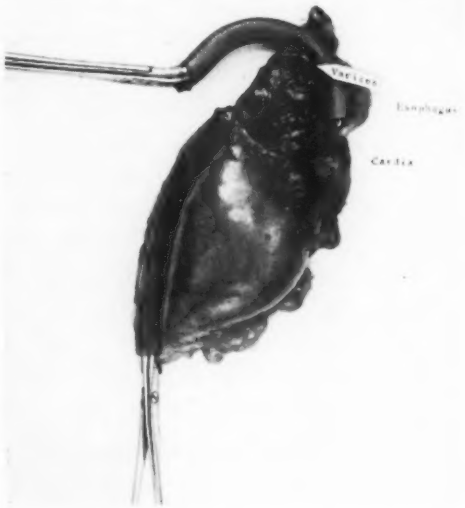

FIG. 4.—Surgically resected lower part of the esophagus and cardia showing marked dilatation and tortuosity of the lower periesophageal veins.

engorgement in the submucosal vessels when varicosed (Fig. 4). While the arteries are less significant than the venous plexus, they too contribute to the alteration in local circulatory dynamics, by bringing blood under pressure into a region from which the efflux is impaired; we consider their ligation and excision an integral part of the proposed plan of surgical management of bleeding varices in selected cases. Removal of these extramural vessels does not compromise the viability of the esophagus, for it is maintained by the smaller intramural vessels that enter the region from above and below.[14]

While admittedly leaving much to be desired, splenectomy has been generally accepted as the single most valuable procedure available for preventing hemorrhage from esophageal varices. Three principal benefits result from splenectomy: first, removal of the enlarged spleen reduces the inflow of blood into the portal bed by 25 to 40 per cent; second, it not only reduces the size

of the portal bed but also interrupts many of the collateral veins which are tributary to the varices about the cardia, esophagus and diaphragm (the sectioning of the vasa brevia is especially important in this regard); and third, splenectomy removes the danger of a secondary panhemacytopenia. Reports by various investigators[7, 10] indicate that some relief from hemorrhagic episodes may be obtained by splenectomy alone in approximately 60 per cent of cases, but complete relief should not be expected in more than 25 per cent of cases. Blakemore[3] and Whipple[25] have pointed out that a permanent cure may be effected with this procedure alone in the usual case in which the splenic vein alone is the site of the portal block.

Vagotomy is performed during the vascular stripping of the lower part of the esophagus. The importance of this procedure in abolishing the cephalic phase of gastric secretion has been emphasized by Dragstedt,[8] Stein and Meyer[18] and others.[16] We are unable, however, to find any previous application of the procedure to the prevention of esophagitis or hemorrhage from esophageal varices. Gastro-enterostomy is performed in order to compensate for the decreased motility of the stomach following bilateral section of the vagi.

REPORT OF CASES

Case 1.—A 27-year-old white woman was seen at the Mayo Clinic in November, 1943, complaining of weakness and left upper abdominal pain of 3 years' duration. She had had poliomyelitis at 2 years of age, with residual affection of the left leg, followed by osteomyelitis of the left femur at 12 years of age, which had required drainage and curettement 4 or 5 times over the next 10 years. A diagnosis of diabetes mellitus was made at 24 years of age. The family history was noncontributory.

The present illness had begun at 16 years of age, when the patient became aware of a sense of weight in the left upper quadrant of the abdomen. Shortly thereafter she had a moderately severe bout of hematemesis and melena. Similar episodes recurred at irregular intervals up to the age of 22 years, when splenectomy was performed elsewhere after a diagnosis of Banti's disease had been made. She had no further bleeding during the succeeding 5 years. Five months prior to admission at the clinic, however, hematemesis and melena of severe degree recurred on two occasions.

A complete physical examination gave normal results in November, 1943, except for residual evidence of the old poliomyelitis. The urine, hemoglobin content, erythrocyte count, sedimentation rate, serum bilirubin level and the results of the serum sulfobromophthalein (bromsulfalein) test of hepatic function were all normal, as were roentgenograms of the chest, esophagus and stomach.

Esophagoscopic injection of the esophageal varices was offered but the patient declined. Upon her return to the clinic 5 years later, in 1948, she stated that she had had approximately ten episodes of hematemesis and melena in the interim. All had required transfusion. Her last episodes of bleeding had occurred 2 months prior to admission and had required 17 transfusions.

A complete physical examination again gave essentially normal results. The urine was normal. The hemoglobin content of the blood was 12.7 Gm. per 100 cc., the erythrocytes numbered 3,870,000 per cubic millimeter, and the leukocyte count was 5400 per cubic millimeter, with a differential count of 32 lymphocytes, 53 neutrophils, 5 monocytes, 8 eosinophils and 2 basophils, all expressed in per cent. The serum bilirubin level was 0 direct and .6 mg. per 100 cc. indirect. The prothrombin time was 19 seconds, and the serum sulfobromophthalein test of hepatic function did not reveal any retention of the

dye. Roentgenograms of the chest, esophagus and stomach were essentially normal. Esophagoscopy revealed esophageal varices in the distal third of the esophagus. The largest of these measured approximately 3 mm. in diameter. Gastroscopy disclosed one dilated vein just inside the cardia, measuring approximately 5 mm. in diameter.

Exploration was carried out through a long, secondary, left subcostal incision. The liver was normal in appearance and the visible tributaries of the portal system were not appreciably enlarged. Cannulation of one of the veins tributary to the splenic vein revealed a venous pressure of 280 mm. of water while the arterial pressure was 130 mm. of mercury systolic and 80 mm. diastolic. In view of the fact that the portal tributaries were too small to permit establishment of a satisfactory venous shunt, an attempt was made to devascularize the lower end of the esophagus. The lower 4 inches of this organ was completely denuded of its surface vessels down to its outer muscular layer. In addition, approximately 5 cm. of each vagus was excised in an attempt to reduce gastric acidity and regurgitation of acid chyme into the lower part of the esophagus. The postoperative convalescence was uneventful, and follow-up 14 months later revealed no recurrence of hemorrhagic episodes.

Case 2.—A 34-year-old white man was seen at the clinic in April, 1949, with a complaint of recurrent episodes of hematemesis and melena of 17 years' duration. His family history and his own past medical history were not remarkable. His present illness had begun 17 years previously when he was awakened by a sense of nausea and soon vomited about 500 cc. of bright red blood. This was followed by melena for the next 2 days. After that he had approximately one episode of melena yearly without other symptoms until 10 years prior to admission, when he had had an episode of melena which persisted for one week. During the 10 years prior to admission he had had two episodes of melena lasting one to two days each. Three months prior to admission melena recurred and continued every day for one month. An examination at home at that time revealed that his spleen was enlarged.

A complete physical examination at the clinic gave normal results except for the finding of an enlarged spleen which could be palpated 5 cm. below the left costal margin. The liver was not palpably enlarged. The urine was normal. Complete blood studies revealed a hemoglobin level of 13.2 Gm., an erythrocyte count 4,560,000, and a leukocyte count of 5900, with a differential count of 55 lymphocytes, 40 neutrophils, 2.5 monocytes and 2.5 eosinophils. The sedimentation rate of the erythrocytes was 18 mm. in one hour, and the prothrombin time was 24 seconds. The serum sulfobromophthalein test of hepatic function revealed an 8 per cent retention at the end of one hour; the serum bilirubin level was 0 direct and 1.2 mg. indirect; the plasma protein level was 7.05 Gm. per 100 cc., with 4.04 Gm. of albumin and 3.01 Gm. of globulin. A roentgenogram of the chest was normal but a roentgenogram of the esophagus and stomach revealed large varices involving the lower two-thirds of the esophagus and the cardia of the stomach, and a duodenal ulcer.

Exploration was done through a left upper rectus incision. The spleen was approximately 6 times the normal size, showed considerable scarring on its external surface, and was adherent posteriorly. The liver was normal in appearance. The veins of the omentum and mesentery were enlarged, and cannulation of one of the omental veins revealed a venous pressure of 300 mm. of water, while the arterial pressure was 140 mm. of mercury systolic and 86 mm. diastolic. Since any attempt at performing a splenorenal venous shunt was prohibitive from a technical standpoint, the spleen was removed and the vessels in its pedicle were ligated individually. Approximately 8 cm. of esophagus was then completely devascularized down to the muscularis and both vagus nerves were sectioned. A supplementary posterior gastro-enterostomy was performed, the proximal loop of the jejunum being approximated to the posterior wall of the stomach near the angle. The patient's postoperative course was uneventful and follow-up 11 months later indicated no recurrence of bleeding episodes.

Case 3.—A 46-year-old white man was seen at the clinic in December, 1949, complaining of recurrent episodes of hematemesis of 9 months' duration. The past medical history and family history were noncontributory.

The patient's present illness began while he was in the army in 1943. At that time he became aware of multiple painful areas, distributed in spotty fashion, over his entire body. Two months later localized painful swelling appeared in these areas which, upon biopsy, proved to be the sites of lipomas. Routine examination of a smear of blood at this time revealed malarial parasites. Following treatment he was discharged from the service. In November, 1948, an anemia for which no obvious cause could be found was detected by his local physician. He improved with general upbuilding until April, 1949, when he had sudden massive hematemesis and required hospitalization. In October, 1949, he had a second episode of hematemesis and melena, and 9 days prior to his visit to the clinic a third episode of severe bleeding had occurred.

Positive physical findings included the presence of multiple tender lipomas over the entire body except the face, legs and feet and an enlarged spleen which could be palpated 3 cm. below the left costal margin. The urine was normal. The hemoglobin content of the blood was 11.2 Gm., the erythrocytes numbered 3,550,000 and the leukocytes 5,900, with a differential count of 78 per cent neutrophils and 22 per cent lymphocytes. The blood sedimentation rate was 30 mm.; the coagulation time was 5.5 minutes and there was clot retraction in 2 hours; the blood platelets numbered 99,000 per cubic millimeter; malarial parasites were not found in smears of the blood, and the serologic reaction of the blood for syphilis was negative; the prothrombin time was 21 seconds; and the serum sulfobromophthalein test of hepatic function failed to reveal any retention of the dye. Roentgenograms of the chest, esophagus, stomach and duodenum were normal. Esophagoscopy revealed several varices of moderate size in the lower few centimeters of the esophagus.

Exploration was carried out through an upper left rectus incision. The spleen appeared to be enlarged about two or three times the normal size and there was marked pulsation and a bruit over the splenic artery. The splenic vein did not appear to be enlarged and there was no evidence of dilatation of the veins which are tributary to the portal vein. The spleen was removed, the splenic vessels being ligated individually. The liver grossly appeared cirrhotic, and biopsy of its edge revealed cirrhosis, grade 2 (on the basis of 1 to 4). The esophagus was mobilized and then devascularized down to the muscularis over its lower 8 cm. of length. Both vagus nerve trunks were sectioned and posterior gastro-enterostomy was done. The patient's postoperative course was uneventful, and follow-up studies 5 months later failed to reveal any history of a recurrence of bleeding.

It is realized that the data obtained from these three cases are inadequate evidence upon which to formulate any definite conclusions, particularly since insufficient time has elapsed since operation. The suggestions have been prescribed only as a preliminary report in the hope that interest may be stimulated and that further experience will sustain the favorable results obtained to date.

SUMMARY

A plan for surgical attack upon bleeding esophageal varices employing the combined procedure of splenectomy, devascularization of the lower part of the esophagus and the cardia of the stomach and bilateral vagotomy and gastro-enterostomy has been suggested. The anatomic, physiologic and pathologic factors constituting the rationale for the proposed plan have been

reviewed. Three cases in which this procedure has been employed with excellent results to date have been reported in detail and in a preliminary manner. A mechanism whereby esophageal varices may originate independent of hypertension in the portal circuit has been suggested.

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DISCUSSION.—DR. LOUIS M. ROUSSELOT: I wish to commend Dr. Gray and his associates for presentation of a new approach to a problem which has interested Dr. Whipple and his students for a great many years.

It is obvious that an intimate knowledge of the natural history of portal hypertension, and the fact that it is a disease of long duration, and an intimate knowledge of the pathology is important in the surgical management of this particular problem. We believe that any therapy which is advocated must be based on a knowledge of the underlying pathology, and should aim to control at least the following two factors: First, the portal hypertension, and secondarily, the associated hypersplenism which is present in nearly all the cases.

It is our opinion that any surgical procedure which does not include splenectomy as a part of the procedure is, therefore, irrational. Furthermore, all cases will not necessarily need a shunting procedure.

The nature and the type of the obstructive factor is important. In thrombotic occlusion, in splenic artery aneurysm, with partial stenosis of the splenic vein, close to the hilum of spleen a shunting procedure is unnecessary.

In the past few years it has been our fortune to have had two cases of splenic aneurysm with the complete so-called Banti picture, with severe hematemeses. Splenectomy alone was elected, and in this type of case will do well, but, as Dr. Gray mentioned, cases with right-sided blocks will inevitably need some combination of procedures, the basic one being splenectomy.

In our own clinic we have been concentrating on combined splenectomy and splenorenal shunt, and to date we feel fairly satisfied with our results, with follow-ups now ranging up to four years.

We feel that this is a problem of such difficulty and with such varying results that it is worth the while of certain groups to concentrate on a larger series of cases, so that they can eventually be intelligently assayed.

It has been my feeling for some time that the concentration on the esophageal varices as the only source of bleeding is to be deplored. In a study of the pathology in these conditions, particularly with right-sided blocks, one frequently sees dilated submucosal vessels in the distal part of the stomach and upper part of the intestinal tract, as well as the esophagus. Likewise, the esophageal varices are not always limited to the lower part of the esophagus, but extend upward in disturbing and alarming fashion for a considerable distance.

Before closing, I should like to call to the attention of the group a single diagnostic procedure that we have found very valuable in the early differentiation of causes of massive gastro-intestinal bleeding when the patient is first seen in the critical state, and that is the taking of a scout film of the left upper quadrant. The observation of splenomegaly is a very valuable diagnostic clue and can oftentimes be noted, even though the severe hemorrhage has decompressed the spleen well below the costal margin. We routinely do this as an adjunct in study of these cases during this critical phase.

Dr. Nathan A. Womack: I should like to present our experience at the University of Iowa with the operation that was recently suggested by Dr. Phemister and Dr. Humphrey for the treatment of massive hemorrhage from large esophageal varices. We have had five such patients who were operated upon, and in all of them the cause of the varices was a far advanced cirrhosis of the liver. It is well that this be stressed, for not only does it mean that the surgical risk will always be great where varices have resulted from such a cause, but also that the surgical therapy which probably will be most effective is that not only directed at the prevention of subsequent hemorrhage but also that which is most effective in supplying adequate nourishment to the liver. This operation, which consists of removal of the lower portion of the esophagus and a considerable part of the stomach along with the spleen, does three things which to me seem to be of great importance. It removes the area of bleeding, it lowers portal hypertension by decreasing the amount of portal flow into the liver, and it relieves the patient of an often incapacitating increase in splenic function. From the physiologic standpoint, therefore, it would seem to me that this procedure is superior to the performance of an Eck fistula.

In the five patients whom we treated, one succumbed while still in the hospital. This was the result of pulmonary embolism. Another patient, a young girl of nine years with far advanced juvenile cirrhosis, survived for one year, dying from what apparently was hepatic insufficiency. The other three patients, a boy of 15 years, a woman of 58 years, and a man of 56 years, have had a most satisfactory postoperative existence for periods ranging from 14 to 23 months. While such a short term follow-up is not too significant, I describe this experience to call attention to the fact that these patients have gained considerable weight and are in a much better nutritional state than they were for some months preceding their operations. One also can stress that while the operation is technically tedious, it also can be made relatively safe. It has brought so clearly to our attention the massiveness of the varicosities and their extension not only about and within the esophagus but also within the submucosa of a considerable portion of the stomach. These findings have served to convince us that at the present time lesser procedures such as the injection of sclerosing substances or the ligation and excision of veins probably will not be too effective.

I think this contribution of Dr. Gray and Dr. Whitesell is a most important one, for in demonstrating another mechanism for the formation of esophageal varices they have shown how essential it is not to group all such venous dilatations under the same cause. As a corollary to this, it becomes obvious that the same operation probably will not fit all patients with bleeding esophageal varices. It will necessitate a more careful differential diagnosis than has been true in times past when confronted with massive esophageal hemorrhage.

Mr. Phillip Rowland Allison: In view of the seriousness of this condition, the perplexities of it, our general ignorance of its causes (and I purposely say "causes") and the natural history of the disease, I would like to make a plea for a very critical attitude to anything we may do to relieve the condition.

The operations that have been performed are variously performed for ascites and bleedings, and yet one finds very frequently that the effect of the treatment is not really adequately related to the patient's complaint.

I take it that if you are operating for ascites, and the ascites disappears after your operation—and if it does so regularly, and not with other operations—then that seems to me to be a fairly good operation, but if you are operating for esophageal varices, the only effective operation is one which either makes them disappear or reduces the tension to an appreciable degree.

Now, try as I may (and it isn't from lack of endeavor), I have never yet heard at a meeting or seen in any literature a description of esophageal varices seen through the esophagoscope before operation, and described as seen through the esophagoscope after operation.

The fact that the patient is alive one or two years after operation, and hasn't bled, carries no weight with me at all, because I think that very often these patients go without bleeding for a long time, particularly after they have been in a hospital and have had transfusions and high-protein diets, and so on. I do feel that, ideally, we ought to be able to measure the pressure in these varices before an operation and afterward, and see what effect it has. In fact, I have now established a setup for doing that, through the esophagoscope. The least we can do, however, without a complicated setup, is to describe the size of the varices before and after operation.

I have nothing to offer in the way of satisfactory treatment for these things, but I have been working along the lines of devascularizing the esophagus from the upper end of the stomach, taking great care to leave intact the vast network of collaterals extending up the mediastinum outside the esophagus. We should remember that these latter veins are a method of getting the blood back to the heart, and therefore they are important, and we shouldn't destroy them; we should only try to obstruct those which are liable to bleed, that is, the submucous ones, and I would point out that we don't really know why they do bleed. You can put large needles into these varices through the esophagoscope, and they ooze, but they don't cause serious bleeding.

Well, with regard to devascularization of the esophagus, I was very hesitant about this for a long time, but I have been gradually extending the devascularization, and I find that it is quite possible to divide every vessel going in and out of the esophagus from the left main bronchus down to the cardia, and to divide every mesenteric vessel going in and out of the upper half of the stomach, and to divide the muscle layers of the esophagus and sever the longitudinal submucous veins going into it, and suture the muscle wall again, and all this without sloughing of the esophagus.

That is what I have been trying to do, and as far as my esophagoscopic observations go, up to now, that is the only thing which has produced any really appreciable diminution in the size of these varices; however, I don't offer it as any more than a tentative suggestion at this stage.

Dr. Emile Holman: Several years ago it was demonstrated that we could ligate the portal vein in dogs completely only if we first provided a collateral circulation. This collateral circulation was developed by implanting the spleen following scarification of its surface in the lateral abdominal wall in a small peritoneal pocket, and by completely dividing the splenic artery. This reversed the flow of blood in the splenic vein, shunting portal blood into the spleen and thence into the collateral bed of the abdominal wall.

This operation has been applied successfully in two patients, one with ascites, and in a patient of 27 who had had many hemorrhages from esophageal varices. The spleen, twice normal size, was implanted in the lateral wall four years ago and the splenic artery ligated. There have been no hemorrhages since.

Dr. Howard K. Gray (closing): The purpose of this presentation has been accomplished, because it was made in the hope that it would stimulate just the type discussion it did stimulate.

I am frank to admit that the procedure as presented to you is the result of desperation and defeatism owing to the fact that, in my brief experience with this problem, I know of nothing quite so difficult to treat, nor any operation quite so difficult to perform as one of the shunts that have been devised.

An attempt was made to find some procedure which from a theoretical standpoint would offer benefit to the patient and at the same time be safe; a procedure that could be carried out by surgeons other than those especially skilled, and still not burn the bridges completely so that one would have nothing to work with should further operative procedures be necessary.

I am deeply grateful to Dr. Rousselot, Dr. Womack, Mr. Allison and Dr. Holman for their comments. I would agree entirely with all of them, particularly with Mr.

Allison, in his viewpoint that the ideal procedure is to reduce the tension in these vessels if at all possible. How? That is the question.

In some instances we have had the privilege of seeing patients wih hemorrhagic esophageal varices in whom there seems to be no change in the visible tributaries of the portal system. The block may have occurred along the splenic artery, that you cannot demonstrate, along the coronary veins, or perhaps in the azygos system.

All of the procedures suggested have value. For those who have had experience with the shunts, we all sincerely hope that they will continue to utilize them and bring to us the great value of their experiences. I agree with Mr. Allison, also, that we wish to retain the collaterals in the attempt to devascularize the esophagus from the upper end of the stomach, but there is certainly no consistency in ligating the coronary vein and thus make bad matters worse in a vessel that is not able to empty itself in the first place. It would seem more reasonable to ligate the vessels that are carrying blood under pressure to the area from which egress is opposed.

Most of you know Dr. Rienhoff has been interested in ligating the hepatic artery in conditions such as we have been discussing. He was called back to Baltimore unexpectedly, but he left a note in my box last night, asking that I mention this study to you. He has ligated the hepatic artery as close to the celiac axis as possible. As is true of any arterial ligation, the closer to the source the ligature is placed the fewer the collaterals that will be interrupted and the more viability that will be retained in the organ supplied by the artery.

The procedure has been used for bleeding esophageal varices in three cases. According to his note, no bleeding in any of those cases has occurred "in this length of time," but he did not mention the length of time. He said it had been used for ascites in four cases. All of these patients were freed of ascites promptly and there has been no recurrence of the ascites in one year for the shortest duration of time since operation, and three years for the longest.

This is a most interesting and intriguing suggestion. The ratio of blood passing through the liver in normal situations is usually about 75 per cent from the portal system and about 25 per cent from the hepatic artery. In cirrhosis that ratio evidently is reversed, with the tremendous disproportion in the amount of blood attempting to pass through the liver, in which the venous channel has been partially blocked in the attempt to reduce the amount of arterial blood so that the veins may empty more effectively, is evidently the rationale behind this procedure.

Dr. Wangensteen has been doing total gastrectomy with the purpose of reducing the regurgitation of gastric chyme into the lower esophagus and diminishing this factor in the production of mucosal erosion. The procedures we have suggested follow in some details the same fundamental principle but are far less radical and can be applied with greater safety.

FRACTIONATED INTRA-ARTERIAL CANCER CHEMOTHERAPY WITH METHYL BIS AMINE HYDROCHLORIDE; A PRELIMINARY REPORT*

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THE INTRAVENOUS INJECTION of Methyl Bis (B-Chloroethyl) Amine Hydrochloride§ has been found to be of clinical value in the treatment of the lymphomas,[6, 9, 20, 24] but of almost no value in the treatment of carcinomas.[14] The success of this treatment for malignant disease has been limited by the damage to the hematopoetic system.[17] Total body irradiation, which is comparable to intravenous HN_2 therapy, has also been used successfully for the lymphomas,[12] but has been of little value in the treatment of carcinomas.[19] Irradiation, however, is a more successful method of cancer therapy because it can be administered in fractional doses to localized tumors without damage to the bone marrow and other vital organs. If the effects of administration of HN_2 could be localized to the region of the tumor, it would be comparable to fractionated irradiation of local tumors, and effective treatment would be possible with minimal damage to normal tissues in other areas.

A method for accomplishing this type of therapy for regional carcinoma was suggested by the result of the accidental administration of HN_2 into the brachial artery of a patient with Hodgkin's disease. An erythema occurred which persisted several days and was followed by vesiculation and ulceration of the hand and forearm. Eventually the intense local reaction subsided and no irreversible changes were observed. This suggested that intra-arterial injection of HN_2 could produce, within the area supplied by the artery, an intense reaction from which normal tissue could recover. It also suggested a new method for treating regional carcinoma which has an accessible arterial blood supply.

The literature contains no reference to the intra-arterial injection of HN_2. However, the technic has been employed successfully for the injection of antibiotics,[8] heparin,[7] and vasodilators.[13]

* Read before the American Surgical Association, Colorado Springs, Colo., April 21, 1950. This investigation was aided by grants from The National Cancer Institute, from The District of Columbia Division of The American Cancer Society, and from The American Cancer Society.

† Fellow in Surgery and Trainee of The National Cancer Institute.

‡ Research Fellow of The National Cancer Institute assigned to The George Washington University Cancer Clinic.

§ Hereafter referred to as HN_2

Intravenous HN_2 exerts some selective action against certain types of cancer in vitro[4] as well as in vivo.[16, 22] Some cases of carcinoma of the lung show a favorable response to intravenous HN_2.[3, 22] Histologic studies of tissues from these cases following HN_2 therapy have demonstrated cellular changes not seen in cancers in other parts of the body. While it is not certain how much of the blood supply of lung cancer is derived from the pulmonary artery as compared to the bronchial artery, the results obtained suggest that the increased concentration of HN_2 received through the pulmonary artery may have been the determining factor in the response obtained. This is closely comparable to intra-arterial therapy, for HN_2 injected into the antecubital vein passes directly into the capillary bed of the lungs. Thus, a cancer of the lung receives a much higher concentration of intravenously administered HN_2 than does a cancer distal to the pulmonary capillary bed. Similarly, by intra-arterial administration, a high concentration of HN_2 could be delivered to tumors elsewhere in the body, and the diluting and detoxifying factors attendant upon intravenous injection could be avoided.

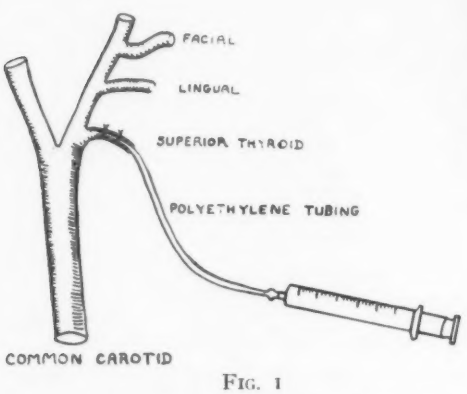


FIG. 1

FIG. 2

FIG. 1.—Diagram illustrating the method of introducing the polyethylene tube into the external carotid artery.

FIG. 2.—Polyethylene tubes in the external carotid arteries, with the stopcocks attached and sutured to the skin of the chest (Case 1).

METHODS AND MATERIALS

A suitable technic was developed by utilizing the method which Donovan[7] devised for intraarterial administration of heparin. This method consisted of the introduction of a polyethylene tube through a proximal arterial branch directly into the artery selected for injection (Fig. 1). The tubing* used had

* Obtained from Anchor Plastics Company, New York, N. Y.

an inner diameter of .042 in. and an outer diameter of .068 in. The polyethylene tubes were prepared by inserting an intravenous needle of suitable size into one end of the tubing. Heating the needle caused the tube to contract firmly around the shaft. A stopcock was then soldered to the needle. In order to prevent the accidental release of the stopcock, all exit openings were closed with detachable connections which had been sealed with solder.

At operation the free end of the polyethylene tube was introduced into the proximal portion of the arterial branch as far as was desired. Silk ligatures were placed around the arterial branch over the tubing. Care was taken not to compress the tubing with the sutures or to injure it in bringing it through the incision. The protruding end of the tube was sutured to the skin to prevent accidental withdrawal (Fig. 2).

Before each injection, the patency of the tube was determined with the physiologic saline. The desired dosage of HN_2 was given into the tube, followed quickly by at least 5 cc. of physiologic saline solution. The nitrogen mustard used was the Methyl Bis (B-Chloroethyl) Amine Hydrochloride.* In each instance, the crystals were dissolved in physiologic saline solution (1.0 mg. per ml.).

ANIMAL EXPERIMENTS AND OBSERVATIONS

Experiments were set up to test the value of intra-arterial nitrogen mustard therapy for cancer.

Comparison between the effects of intravenous (total body) and intra-arterial (regional) HN_2 therapy on tissues of rabbits and dogs. In rabbits a single intravenous injection of HN_2 (1 mg. per Kg. of body weight) produced no gross changes in the extremities. However, a single intra-arterial injection of HN_2 (0.1 mg. per Kg. of body weight) into the femoral artery of each of six rabbits produced, three to five days later, demonstrable swelling and redness in the limb supplied by the injected artery. Within seven days after the injection, vesiculation and ulceration appeared over the distal portion of the extremity. This persisted for several weeks but subsequently healed.

Similar experiments were conducted on dogs. A single intravenous injection of HN_2 (0.1 mg. per Kg. of body weight) produced no gross changes in the skin, muscle, or extremities of the dog. A single intra-arterial injection of the same amount of HN_2 into the lingual artery of each of two dogs produced, three to six days later, marked edema in the portion of the tongue supplied by the injected artery. In 12 days, tissue destruction in the muscle and the epithelium was evident.

The effect of intra-arterial HN_2 on the Brown-Pearce tumor in rabbits. In order to test the degree of selectivity of HN_2 for neoplastic tissue in an animal in which the regional blood supply would be accessible for injection, the Brown-Pearce tumor in rabbits was selected. Brown-Pearce tumor was

* Supplied by Merck and Company as "Mechlorethamine Hydrochloride."

inoculated into the testes of 36 rabbits. When the tumors were large enough to be palpated, a single injection of HN_2 (0.1 mg. to 0.2 mg. per Kg. of body weight) was given into the abdominal aorta just above the orifices of the renal and spermatic arteries. The aorta was compressed distal to these vessels during the injection. Seven to ten days later the animals were killed and examined. Necrosis was present in all the treated tumors. The kidneys showed no histologic damage.

The effects of repeated intra-arterial injections of HN_2 on non-neoplastic tissues. Polyethylene tubes were inserted into the lingual arteries of normal dogs. One dog received five injections of HN_2 (0.2 mg. per Kg. of body weight) into the lingual artery at 24-hour intervals. Ulceration and necrosis of the tongue appeared on the tenth day. This destructive process was sharply limited to the ipsolateral tongue when the animal was killed and autopsied on the fourteenth day. Histologically, the lingual epithelium on the injected side was necrotic to the midline. At that point, there was a distinct line of demarcation between necrotic and normal epithelium. The demarcating line extended throughout the thickness of the tongue as a dark blue zone of necrotic and inflammatory tissue. On the untreated side, the tissue was normal except for hyperemia of the subepithelial vessels. On the injected side, all the tissues were necrotic, except for the fat, which had not been altered. The arterioles contained organizing thromboses, but the large arteries showed no change.

A second dog received six injections of HN_2 (0.1 mg. per Kg. of body weight) into the lingual artery at 24-hour intervals. The dog was killed and autopsied at the end of 14 days. The only pathologic finding was intense hyperemia of the ipsolateral tongue. Microscopically the lingual epithelium was intact on both sides. On the treated side, the underlying connective tissue showed moderate hyalinization. The muscle cells were shrunken and pale; and their nuclei were large, hyperchromatic, and irregular. Edema and small scattered areas of hemorrhage were present. Foci of inflammatory cells were scattered through the fatty tissue. The large arteries were normal, but the intima of the arterioles was thickened, and thromboses were present.

A polyethylene cannula was introduced into the internal carotid artery of each of five dogs, and 1 mg. of HN_2 was given every 24 hours for four to ten days. The injections produced no apparent pain or immediate effect. Within 72 hours, each dog had developed an enophthalmos, palpebral narrowing, and a suggestion of facial paralysis on the treated side. No convulsions were noted. The dogs would not eat after seven days but otherwise seemed in good health. At autopsy, the treated cerebral and cerebellar hemispheres were smaller, the superficial vessels more dilated, and the convolutions more flattened.

On cut section, soft, dark red areas were noted in the region of the basal ganglia. There was no change in either the cortex or the white substance except for the dilatation of vessels on the injected side. The only microscopic change in the injected hemisphere was hemorrhagic necrosis of the entire head

of the caudate nucleus and of the hypothalamus near the substantia nigra and the putamen. There was no change in the ependyma. There was no evidence of extra-cranial lesions or damage.

A polyethylene tube was introduced into femoral artery in each of two dogs, and 1 mg. of HN_2 was injected every 24 hours. After 48 hours, the hair on the treated leg could be plucked easily in large amounts, and the leg muscles were weak, although good arterial pulsations were present. One animal died in four days of peritonitis resulting from ischemia of the bowel due to inadvertent trauma to the mesentery at the time of operation. The second dog was killed and autopsied in ten days. No gross changes were apparent in the treated leg of either dog.

DISCUSSION

There was no available method of measuring the amount of the reactive HN_2 absorbed by the tissues, but it was possible to determine the effects of HN_2 by histologic study of tissues. The findings in these experiments were convincing, and the results were distinct and reproducible. It was apparent that intra-arterial injection of HN_2 produced, within the areas supplied by the injected arteries, tissue changes which cannot be produced by intravenous injection of lethal amounts of the drug.

In determining the degree of selectivity of HN_2 for neoplastic tissue, it was recognized that the Brown-Pearce tumor was not entirely satisfactory because of the high incidence of spontaneous necrosis. Though many animals would be required for quantitative studies to determine dosage, the constant presence of necrosis in all treated tumors, in the absence of damage to treated kidneys, indicated that there was a favorable selective action on this tumor.

The tissue response to HN_2 has been stated to be similar to that of irradiation.[10, 15] A single massive intra-arterial injection of HN_2, like a single massive dose of roentgen ray, produces complete destruction of all the treated tissues except fat and large blood vessels. A smaller dose of roentgen ray destroys only certain types of tissue. Repeated small doses of roentgen ray show even greater selectivity.[5] Because of the similar results obtained by the two types of massive dose therapy, an attempt was made to reproduce the selectivity of fractionated irradiation by repeated intra-arterial injections of small doses of HN_2. The results indicated that, by this chemotherapeutic fractionation, it was possible to produce in normal tissue, changes which are similar to those produced by fractionated irradiation.[18] The results also suggested the possibility that a cancerocidal dose of HN_2 might be delivered to a tumor by regional administration without producing local ulceration or necrosis of adjacent normal tissue.

CLINICAL TRIALS

The preliminary evidence of selective action of HN_2 by intra-arterial administration and the establishment of "safe" fractionated dosage levels in rabbits and dogs provided the basis for further studies on cancer patients.

This report covers the immediate results obtained in the first ten patients treated. We have excluded three patients who died from complications of their cancer within the first 24 hours of treatment. Results are tabulated on Tables I, II, and III.

The cases fall into three groups according to the anatomical region in which the tumor was located. Seven patients had cancer of the head and

TABLE I.—*Summary of Intra-Arterial HN_2 Therapy.*

Case	Pt.	Diagnosis	Previous Therapy	HN Therapy Total mg.	mg. Kg.	Dose Schedule	No. Days	Artery Cannulized
1.	J.H.	Epidermoid Ca. of upper lip metastatic to submaxillary glands	Surgery and Roentgen ray	76.7	1.47	1.3 mg. q. 8 hrs.	11	Rt. external carotid via superior thyroid
2.	J.S.	Epidermoid Ca. of soft palate	Surgery	41.0	1.10	1 mg.q. 24 hrs. then q. 12 hrs.	22	External carotids via rt lingual branch and left superior thyroid
3	L.L.	Epidermoid Ca. antrum metastases to submaxillary glands	Surgery and Roentgen ray	39.0	0.53	1.5 mg. q. 12 hrs.	12	Left external carotid via superior thyroid
		(2nd course 4 days after 1st)		41.0	0.55	2.0 mg. q. 8 hrs.	7	Rt. ext. carotid via lingual br.
4.	S.V.	Epidermoid Ca. right antrum with extension to palate and orbit and ethmoids	None	57.0	0.90	1.5 mg. q. 12 hrs. then 2.0 mg. q. 8 hrs.	11	Right external carotid via superior thyroid
	C.G.	Epidermoid Ca. of mouth with metastases to submaxillary glands	None	15.0	0.23	5.0 mg. q. 12 hrs.	7	Left external carotid via superior thyroid
		(2nd cour.e 15 days after 1st)		50.0	0.76	2.0 mg. q. 8 hrs.	9	Left superficial temporal.
6.	D.M.	Epidermoid Ca. of right antrum	None	20.0	0.36	1.0 mg. q. 8 hrs.	7	Right external carotid via lingual
7	B.B.	Epidermoid Ca. of mouth with metastases to submaxillary glands	Surgery	16.0	0.20	1.0 mg. q. 8 hrs.	6	Left external carotid
		(2nd course 13 days after 1st)		10.0	0.12	.5 mg. q. 8 hrs.	7	Superficial temporal
8.	D.L.	Fibrosarcoma of right thigh with metastases to lung	Surgery and Roentgen ray	122.4	2.45	2.5 mg. q. 12 hrs. then 3.3 mg. q. 8 hrs.	15	Right iliac via deep epigastric
		(2nd course 6 days after 1st)		32.9	0.66	2.5 mg. q. 8 hrs.	6	Right iliac via deep epigastric
9.	S.W.	Ca. of breast with cerebral metastasis	None	13.5	0.25	0.5 mg. q. 8 hrs.	16	Left common carotid via superior thyroid
10.	G.H.	Glioblastoma multiforme	Surgery and Roentgen ray	21.0	0.31	0.5 mg. q. 8 hrs.	14	Left internal carotid via superior thyroid

neck region supplied primarily by the external carotid arteries. Two patients had brain tumors supplied primarily by the internal carotid arteries, and one had a sarcoma of the extremity supplied by the femoral artery. The following case reports are representative of each respective group.

Case 1.—(J. H.): *Squamous carcinoma metastatic to both sides of the neck.* This 60-year-old colored male first noted a small ulcer on the upper lip in December, 1948. At the time of examination, July, 1949, a large fungating lesion had replaced two-thirds of the upper lip, and there were bilateral enlarged submaxillary lymph nodes. A biopsy

TABLE II.—*Effects of HN_2 Therapy.*

Case No.	Pain	Gross Changes in Lesion	Parasympathomimetic Changes	Gross Radiomimetic Changes	Course
1.	Uncontrollable prior to therapy. No analgesics required 16 hours after treatment.	Softening of tumor with discharge of necrotic material followed by partial healing.	Marked salivation. Miosis.	Erythema of face up to eyes; swelling of tongue and salivary glands. Localized depilation of scalp.	Died 89 days following institution of therapy.
2.	Severe pain in neck and throat completely relieved in 48 hours.	Regression in size of lesion.	Moderate salivation. Weakness.	Mucositis of pharynx and soft palate.	Died on 25th day from massive pulmonary embolism.
3.	Persistent prior to treatment. Complete relief in 96 hours. Developed painful area on palate during therapy.	Softening and flattening of lesion by 6th day. Discharge of necrotic material through sinus tract.	Moderate salivation. Weakness?	Mucositis soft palate. Facial erythema.	Died 33 days following institution of therapy. Cachexia and terminal pneumonia.
4.	Frontal headache diminished in 48 hours, disappeared in 72 hours.	Ulceration and sloughing followed by shrinkage of oral, nasal and orbital mass.	Marked salivation. Skin right side of face warm and dry.	Mucositis. Dysphagia, hyperemia and edema of face.	Died on 26th day. Aspiration pneumonia?
5.	No pain prior to first course of therapy. Subsequent pain relieved by second course.	Softening and shrinkage of lesion; especially of neck nodes.	Excessive salivation. Skin of face warm and dry.	Hyperemia side of face followed by pigmentation and scaling.	Died 38 days following institution of therapy. Cause of death?
6.	Mild pre-treatment pain disappeared.	Reduction of lesion to less than one-half of original size.	Increased salivation. Skin right face warm and dry.	Small area of mucositis of hard palate. Local erythema.	Living 40 days after institution of therapy. Condition improved.
7.	Pain disappeared in 48 hours.	Ragged, bleeding tumor became smooth; bleeding stopped; reduced to ¼ of original thickness.	Excessive salivation.	Erythema over lower face. Mild mucositis.	Living 28 days after institution of therapy. Condition improved.
8.	None	Tumor became soft and cystic.	Skin of treated extremity warm and dry. Increased weakness of foot questionable.	Erythema followed by vesicle formation. Depilation.	Died 29 days after institution of therapy. Cachexia.
9.	None	Could not be observed. Visual fields increased in size.	?Transient hemiplegia.	None.	Living 68 days after institution of therapy. Condition satisfactory.
10.	None	?Reduction in size and tension of subtemporal decompression.	None.	None.	Living 23 days after institution of therapy. Condition fair.

from the upper lip showed squamous carcinoma. On August 12, resection of the upper lip and bilateral upper neck dissections were performed. Histologic examination showed squamous carcinoma of the upper lip with metastasis to the submaxillary nodes bilaterally. For 3 months the patient was clinically free of disease. Recurrence was then noted both at the angle of the left mandible and in the right submaxillary region.

Roentgen ray therapy was started, but because the patient was unco-operative it was discontinued after he had received only 400 R. to each side of the neck. The tumor continued to grow rapidly and by November 25 he could swallow liquids only. Roentgenograms of the mandible demonstrated a large area of destruction in the posterior third of the horizontal ramus of the left mandible. Marked trismus limited the bite to a width of 2 cm.

TABLE III.—*Hematologic Effects of HN_2 Therapy.*

Case No.	W.B.C. Control	W.B.C. Lowest	W.B.C. Day	R.B.C. Control	R.B.C. Lowest	R.B.C. Day	Platelets Control	Platelets Lowest	Platelets Day	Bone Marrow Maximum Depression Day	Bone Marrow Maximum Depression Cellularity	Bone Marrow Maximum Depression % Maturation MN	E.S.R. mm./hour Before Therapy	E.S.R. mm./hour After Therapy
1.	12,500	1,200	13	4.41	3.33	6	315,240	53,100	22	10	++	4	40	28
2.	6,200	No fall		3.84	No fall		130,120	47,400	24	20	+++	56	11	30
3.	9,100	5,000	13	4.17	3.74	6	555,900	185,000	5	12	++	17	30	..
	*9,250	1,250	10	4.72	4.20	6	325,500	125,000	6	8	+	60	..	..
4.	5,600	800	20	4.22	3.78	16	144,520	64,530	19	14	+	74	21	23
5.	5,650	5,600	14	4.31	3.52	6	160,090	91,520	6	31	++	20.8	36	37
	*7,600	450	13	3.91	3.48	12	137,720	59,630	12	8	++	78.6	..	31
6.	5,700	6,300	8	4.28	3.96	8	175,480	153,500	6	No depression			32	34
7.	14,350	12,400	12	4.08	3.30	16	248,900	131,100	2	No depression			30	34
	*17,600	10,450	9	3.73	3.55	2	160,800	248,500	4	No depression			34	32
8.	13,700	3,950	18	3.97	3.05	14	177,100	42,540	10	13	++	51	34	32
	*3,950	1, 50	8	4.04	3.35	5	64,500	41,500	2	7	+	10	26	..
9.	7,300	6,450	12	4.35	3.72	5	243,900	179,000	14	No depression			41	48
10.	6,450	7,800	7	5.83	4.41	10	245,000	113,070	10	No depression			9	34

* Second course of therapy.

On November 27 the patient was admitted to The George Washington University Hospital. During the preoperative period he walked the floor and cried with intractable pain. On December 2, under general intratracheal anesthesia, a vertical incision was made along the anterior border of the right sternocleidomastoid muscle which was divided transversely. The external carotid artery was exposed, and its superior thyroid branch isolated and divided 2.5 cm. from its origin. A polyethylene tube was threaded, through the proximal portion of the thyroid tributary, into the external carotid artery and held in place by 3 silk ligatures. The tube was secured to the skin with a stitch ligature and the wound was closed with silk. The same procedure was carried out on the left side (Fig. 2).

Beginning 6 hours after the operation, 1.3 mg. of HN_2 (.025 mg. per Kg. of body weight) was injected into each polyethylene tube at intervals of 8 hours. This routine was continued for 10 days on the right side and 11 days on the left side for a total dose of 76.7 mg. Following each injection the patient experienced no pain, but occasionally complained of discomfort in the scalp. This was relieved by injecting 1 to 3 cc. of 1 per cent procaine into the tube. The right tube became plugged and was withdrawn on the tenth day without evidence of arterial bleeding. The left tube remained patent for 25 days.

Daily injections of physiologic saline were made after the eleventh day. An elective tracheostomy was performed on the eleventh day.

Serial biopsies obtained from the tumor in the left neck, every 2 days for 14 days and weekly thereafter, were studied microscopically to evaluate the effects of treatment on the tumor.

SUMMARY OF THE EFFECTS OF TREATMENT IN CASE 1

Effect on Pain. Within 16 hours after the first injection there was complete relief of pain and the patient no longer required opiates. Codeine was given for an occasional "headache."

Changes in Gross Appearance of the Cancer. (Figs. 3-6.) Before therapy, each ulceration on the neck had a firm, ragged, grey center and a hard, elevated, rolled edge. By the fifth day of treatment, each area of ulceration had enlarged, the rolled edge had disappeared, the tumor had softened, and the discharge was copious. By the ninth day, a sinus tract which extended into the left mandible was noted. By the eleventh day, both areas of ulceration had decreased in size. By the twenty-eighth day, healing was almost complete on the right side. However, on the left side residual carcinoma was present on the lower medial portion of the defect. This was the portion of the tumor supplied by branches of the superior thyroid artery which had been divided in cannulating the external carotid artery. No other active disease was apparent at this time. The sinus tract extending into the mandible remained.

Roentgenograms of the left mandible showed an increase in the area of destruction during the first 2 weeks of therapy, but no further increase in the next 8 weeks.

Gross Radiomimetic Changes. A slight reddish color appeared over both sides of the upper neck after three days of HN_2 therapy. The color was more intense after 5 days, and extended up to the lower eyelid on the left side to the malar bone on the right side. It persisted throughout the therapy and then slowly disappeared. Dysphagia developed on the fifteenth day, and tube feedings were required from the nineteenth to the twenty-fourth day. Painless trismus prevented adequate examination of the pharynx, but the dysphagia was attributed to edema. There was marked swelling over both parotid glands, and the tongue became tender and swollen after 8 days of therapy. The pressure of the swollen tongue against the 2 remaining lower teeth resulted in areas of necrosis which healed but left clean notches. The patient's beard ceased to grow, coincidental with the appearance of the erythema, and the hair of the scalp began to fall out one week later. By the twenty-fourth day, all the hair on the face and scalp was lost except for an inch-wide strip of sparse hair in the midline of the chin, lips, scalp, and the back of the neck. Even this had disappeared by the thirtieth day (Fig. 7).

Parasympatho-mimetic Changes. Increased salivation appeared on the eighth day and persisted for a month. Being unable to swallow, the patient drooled copiously. Atropine had no effect on reducing the amount of saliva.

Examinations of the eye were made periodically and no changes were observed in the fundi or cornea during or after therapy. One per cent Paredrine was effective in dilating the pupils until the twenty-sixth day, when it became necessary to use a more potent mydriate (10 per cent Neosynephrine).

Hematologic Changes. The hemoglobin and red cell count showed a moderate decline and then stabilized. This was coincidental with an increase in plasma volume which was attributed to increased fluid intake following relief of pain.

Two weeks after the initial injection, a mild macrocytic hypochromic anemia developed. The reticulocyte count remained normal. The platelet count began to fall by the sixth day, but remained above 100,000 until the twenty-fourth day, when it declined to 53,000. It remained low for 3 days, after which it returned to normal levels. The circulating lymphocytes were decreased in number within the first 24 hours. The few eosinophils noted in the first blood smears had completely disappeared by the third day. The total peripheral white count fell to 1200 on the fifteenth day and remained low for the next 11 days. The sedimentation rate was decreased during therapy and the serum protein levels diminished slightly. Calculation of total circulating protein indicated a slight increase in the albumin fraction and a decrease in the globulin fraction.

Bone marrow specimens were obtained twice each week. Eosinophilic leukocytes decreased markedly within one week. On the eleventh day, cellularity decreased from an

FIG. 7

FIG. 4

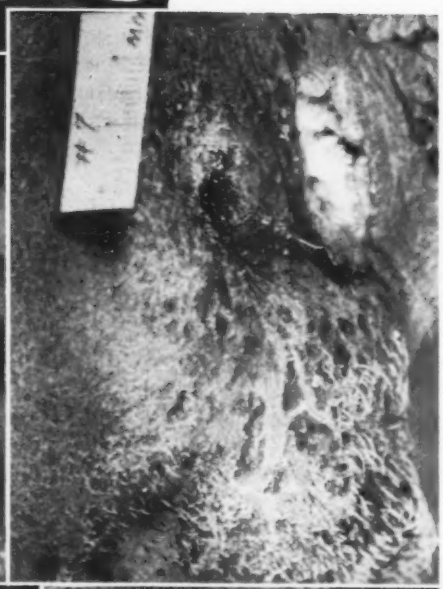


FIG. 6

FIG. 3

FIG. 5

(Legends on opposite page)

original four plus, to two plus. This persisted until two weeks after therapy ended, when the bone marrow first showed evidence of return toward normal as well as an increase in number of eosinophils.

Microscopic Changes in the Cancer. The pre-treatment biopsies showed a grade II squamous carcinoma. The tumor showed a tendency to keratinize and form epithelial pearls. The cells grew in large sheets, interspersed with keratinized masses heavily infiltrated by neutrophils, lymphocytes, and a few plasma cells. Normal mitotic figures were abundant (Fig. 8).

The biopsies, taken at intervals of 48 hours, all contained carcinoma but showed an increased amount of degeneration in successive specimens (Figs. 9, 10).

The first changes observed occurred after two days of treatment and consisted of slight intracellular edema, slight clumping of the nuclear material, and dilatation of blood vessels. In subsequent biopsies, intracellular edema increased and cell cytoplasm became pale pink and cell outline indistinct. Many small cytoplasmic vacuoles appeared and gradually enlarged throughout treatment. Neutrophils appeared in some of the vacuoles which almost filled the cells, compressing the nuclei into demilunes. A few of the enlarged cells, however, were well delineated by condensation of the peripheral cytoplasm. After ten days of treatment, the nuclei gradually enlarged, becoming more hyperchromatic with complete loss of detail and finally karyorrhexis occurred, and complete degeneration of the cells.

The total number of cancer cells per field was reduced approximately one-half after 6 days of treatment. The total number of mitoses per field was reduced by more than one-half after 4 days of treatment and most were bizarre forms. No mitotic figures were seen after 8 days of treatment and, after 12 days, the serial biopsies contained very few cancer cells, the tissue being composed of loose strands of edematous fibrous tissue, keratin and debris. Those cancer cells present were pale-staining epithelial cells which contained blue-grey homogenous karyorrhelic masses of nuclear material. Increasing amount of keratin and debris appeared in the biopsies throughout treatment, associated with an infiltration of lymphocytes and neutrophils.

Following 2 days of treatment, edema of the endothelial cells was the only vascular change. After 4 days of treatment, this appeared more marked and the intima of the arterioles became hyalinized.

At this time, a distinct halo of edema developed about these vessels. Subsequently, thrombosis occurred in most of the medium-sized arteries, followed by infiltration of lymphocytes and neutrophils. The larger arteries did not appear altered and the veins and capillaries showed only swelling of the endothelium.

The epithelium covering the treated area remained unchanged except for slight edema. Normal mitoses were present in the basal layer of the skin in all post-treatment biopsies. After the fourth day, the dermis showed progressive edema coincident with a lymphocytic infiltration. The fibrocytes became edematous and their nuclei hyperchromatic. These changes were more marked about the dermal arterioles.

CLINICAL COURSE

The first six injections of HN_2 caused nausea and vomiting. An unexplained temperature of 102° began on the twelfth day and continued at this level for the next six

FIG. 3.—Ulcerating, metastatic squamous carcinoma of right side of neck, before treatment (Case 1).

FIG. 4.—Ulcerating, metastatic squamous carcinoma of left side of neck, before treatment (Case 1).

FIG. 5.—Right side of neck 25 days after the beginning of therapy, showing almost complete healing of the ulcer (Case 1).

FIG. 6.—Left side of neck 21 days after beginning of therapy, showing partial regression of the portion of the ulcer supplied by the injected artery (Case 1).

FIG. 7.—Loss of hair following injections of HN_2 into both external carotid arteries (Case 1).

days. The patient was discharged from the hospital on the forty-sixth day. Roentgen ray therapy was later administered to the recurrent cancer in the left anterior neck, but he refused to co-operate and treatment was discontinued after 600 R. had been given. After this, he received 10, 10, and 5 mg. of HN_2 intravenously over a ten day period. Following this, the mass decreased in size, but the gross changes were not comparable to those which had been seen following the intra-arterial injection of the same amount of HN_2 He developed dysphagia, became weaker and was re-admitted to the hospital on February 21, where he died 4 days later. He was free of pain to the time of death.

FIG. 8

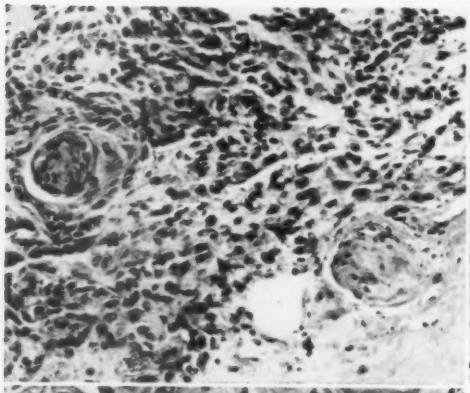


FIG. 9

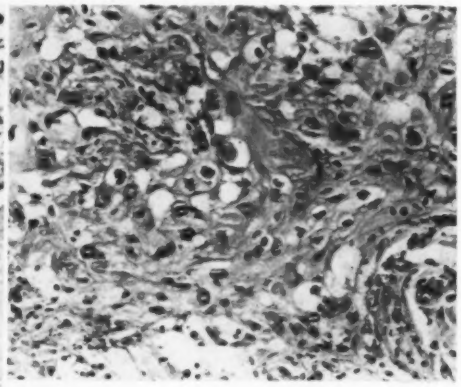


FIG. 10

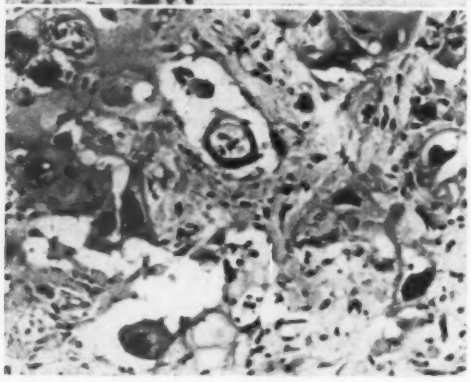


FIG. 8.—Pre-treatment biopsy of squamous carcinoma, Grade II, with tendency to keratinize and form epithelial pearls and intracellular bridges x 160 (Case 1).

FIG. 9.—Biopsy after four days of treatment, showing marked intracellular edema and cytoplasmic vacuolization with nuclear hyperchromatism. x 160 (Case 1).

FIG. 10.—Biopsy after 12 days of therapy. The few remaining cancer cells are represented by large, irregular nuclear masses within thick-walled cells. These are embedded in a mass of degenerating keratin material and debris. x 160 (Case 1).

At autopsy, no tumor was found in the right side of the neck or in the left posterior region of the neck, either grossly or microscopically. Cancer was present in the untreated left anterior portion of the neck. Death was attributed to malnutrition and terminal pneumonia.

Case 2.—(S. W.) *Carcinoma, Metastatic to the Left Temporal Lobe.* This 30-year-old colored female was admitted on January 9, 1950. Her history was considered unreliable. Four months prior to admission she had discovered a lump in the left breast. One month prior to admission, she had noted a "glare" in the right eye and a decrease in

visual activity in both eyes and had suffered a convulsion, followed by a long period of coma. A clinical diagnosis of cancer of the breast with metastasis to axilla and brain was made. She was considered unsuitable for craniotomy.

On physical examination, she was drowsy. There was, in her left breast, a 9 by 5 by 5 cm. mass, in the upper outer quadrant, attached to the skin over a 4 cm. area. There were multiple hard axillary nodes in the left axilla. Aspiration biopsy showed carcinoma.

Her vision was 20/50. There was a paralysis of the right sixth cranial nerve. The left pupil was smaller than the right. There was no papilledema, no atrophy of the discs, but some muscular degeneration. There was a marked visual field defect (Figs. 11, 12).

Neurologic examinations were done by Dr. J. M. Williams. On admission, the patient was oriented as to the time and place. Spinal tap revealed an initial pressure of 380 mm. of water. No other abnormalities were noted.

On January 13, polyethylene tubing was inserted through the superior thyroid artery into the common carotid, and the external carotid artery was ligated beyond the orifice of the superior thyroid artery.

HN_2 (0.5 mg.) was injected every 12 hours for a total of 13.5 mg. Crysticillin (300,000 units) was given daily.

Visual fields enlarged (a malingering target was used) and the initial 15° limitation increased to a maximum limitation of 50° in 12 days (Figs. 13, 14). At this time unaccountable personality changes appeared and made the determination of further visual fields unreliable, so therapy was discontinued. The spinal fluid pressure was recorded at 170 mm. on the eighth day and at 280 mm. on the fifteenth day. Although unable to read during the period of hospitalization, she became able to read newspaper print one month later; the sixth cranial nerve paralysis had become less apparent.

The injection of HN_2 produced a mild transient burning sensation along the course of the internal carotid artery. On the sixth evening, a temporary lethargy appeared immediately after the injection. On the seventh day, sensory aphasia occurred after the injection and persisted for 48 hours. She gave an identical answer to all questions. However, she seemed to know the correct answer without being able to say it. On the ninth evening, a transient right hemiparesis appeared immediately after the injection. Motor control returned in the leg within 5 minutes, in the face within 10 minutes, and in the right arm within 15 minutes. A transient hemiparesis occurred again on the eleventh day. On the fourteenth day, it occurred following an injection of Thorotrast. On the eighteenth day, the cervical sympathetic nerves were blocked with procaine and a single injection of HN_2 was given. The hemiparesis recurred and persisted for 10 minutes.

During the entire period of hospitalization, the patient was ambulatory, fed herself and was free of pain. The primary cancer increased in size during treatment.

Hematologic Changes. No leukopenia or depression of bone marrow occurred. Blood volume was unchanged. The erythrocyte sedimentation rate rose from 41 to 48.

Case 3.—(D. L.) *Fibrosarcoma of Right Thigh, with Metastasis to the Left Lung.* This 61-year-old white male discovered a painless "lemon-sized" mass on the medial aspect of his lower right thigh in December, 1948. Local excision and histologic examination showed it to be a fibrosarcoma. The patient refused radical surgery. Within 2 months a recurrent nodule developed, was excised, and was proved to be fibrosarcoma. Five months later another nodule developed which, by September, had enlarged until it occupied the entire medial aspect of the right thigh. Amputation was again refused, so roentgen ray therapy was given. This consisted of a tumor dose of 1600 R. The tumor continued to grow. In December, 1949, chest roentgenogram revealed a large solitary metastasis in the left lung field. The patient was admitted to The George Washington University Hospital in January, 1950.

On physical examination, he was emaciated and weak. A large solid tumor mass occupied the entire postero-medial aspect of the right thigh. The circumference of the right thigh was three times that of the left. The skin over the tumor was taut and ulceration appeared imminent. Numerous patent dilated veins were visible beneath the skin.

FIG. 11

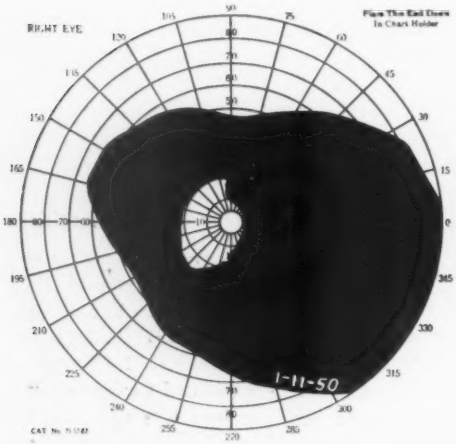
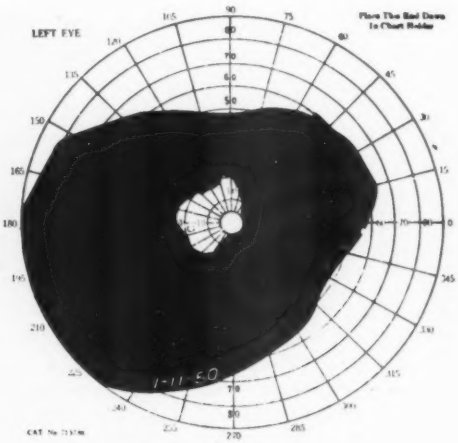


FIG. 12



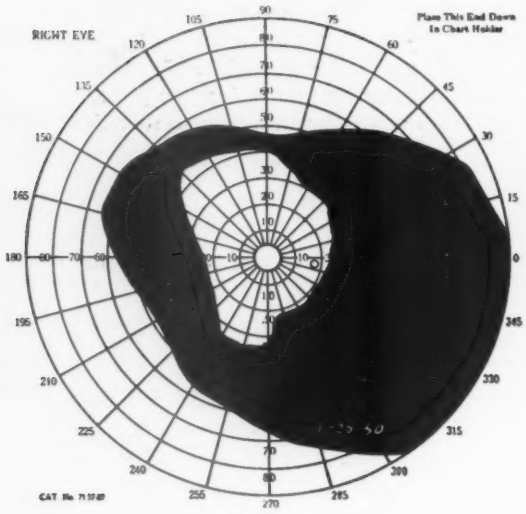


FIG. 13

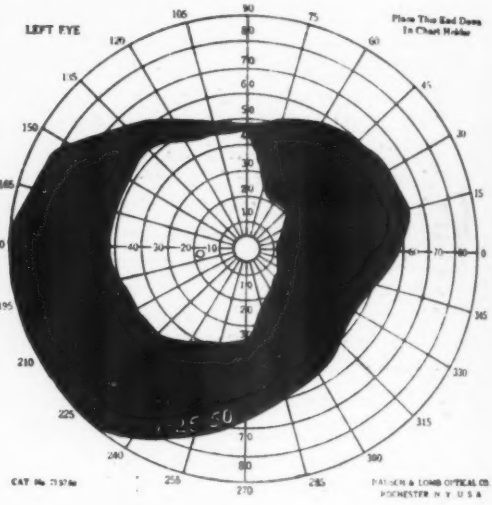


FIG. 14

FIG. 11.—Visual fields before treatment (Case 2); right eye.
FIG. 12.—Visual fields before treatment (Case 2); left eye.
FIG. 13.—Visual fields after treatment by injection of HN_2 into the left internal carotid artery (Case 2); right eye.
FIG. 14.—Visual fields after treatment by injection of HN_2 into the left internal carotid artery (Case 2); left eye.

Marked pitting edema was present in the lower leg and foot. The weight of the left leg prevented ambulation, but there was no pain.

On January 27, a polyethylene tube was inserted through the deep epigastric artery into the right iliac artery, by Dr. A. Horowitz. Injections of HN_2 (2.5 mg.) were given

every 12 hours for 4 days, then increased to 3.3 mg. every 8 hours for a total dose of 122.4 mg. One week later, a second course was given consisting of 2.5 mg. every 8 hours for a total of 32.5 mg.

Effect on pain. The lesion was completely painless.

Gross changes in lesion. In 6 days, the tumor had softened and the skin was movable over it. In 14 days, the tumor felt cystic and a fluid wave could be demonstrated. A trocar was inserted into the tumor and 2300 ml. of viscous brown fluid were withdrawn. The cavity thus produced filled immediately with blood, and the patient went into shock which was controlled by the administration of 2500 ml. of blood. Thereafter, ulceration occurred and drainage was profuse.

FIG. 15

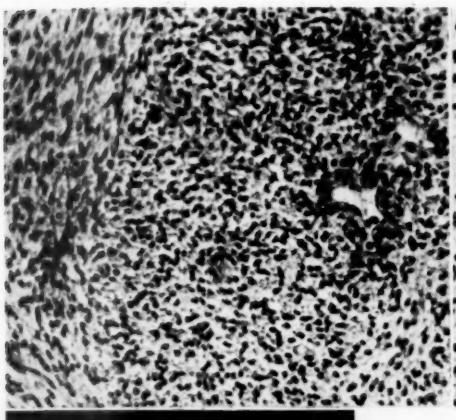


FIG. 16

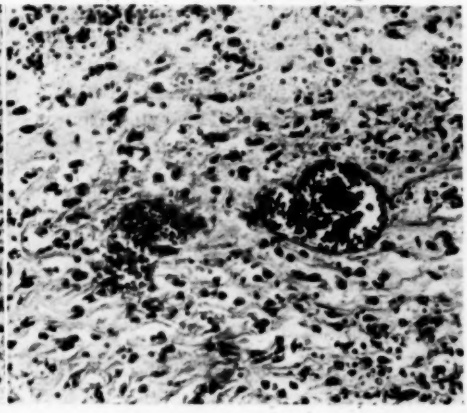


FIG. 17

FIG. 15.—Spindle cell sarcoma of the right thigh, before intra-arterial HN_2 therapy. x 175. (Case 3).

FIG. 16.—Spindle cell sarcoma, following intra-arterial HN_2 therapy. x 175. (Case 3).

FIG. 17.—Alopecia limited to the area supplied by the occipital artery. The superficial temporal branch had been compressed during injection of HN_2 into the left external carotid (Case 3).

The lung metastasis increased in size during treatment.

Parasympathomimetic Changes. After the first few injections, the treated leg became warm and dry and there was a questionable increase in weakness of the muscles of the lower leg.

Radiomimetic Changes. After 6 days of therapy, hair could be removed easily from the calf but never fell out spontaneously. After the first course of therapy, a few small vesicles appeared on the thigh and lower leg. During the second course of therapy, an erythema developed over the thigh.

General Clinical Course. The HN_2 injections produced no nausea, vomiting, or pain. A low grade fever began during the second week of therapy and subsided immediately after the last injection of HN_2. Diarrhea developed on 2 occasions but was controlled easily with paregoric. During the 4 days before death, the blood pressure was 70/50.

The patient became progressively weaker, the skin was extremely pale; fecal and urinary incontinence developed. Just before death he became comatose and the temperature rose to 104° F. The last injection was given 5 days prior to death.

Microscopic Changes in the Tumor. The original tumor consisted of small, closely packed, spindle-shaped cells with indistinct cell membranes. The cells contained a small amount of clear cytoplasm and large deep staining, coarsely granular nuclei. Mitoses were frequent. There was no necrosis and the blood vessels were patent. The diagnosis was spindle cell sarcoma (Fig. 15).

At autopsy, the tumor consisted of a 4 cm. shell surrounding a multiloculated cavity. Only the lower pole of the tumor showed no central necrosis. The solitary lung metastasis was solid throughout. Microscopic sections of the tumor, obtained at autopsy 22 days after the first injection, showed large areas of necrosis, much debris, and had little resemblance to the untreated tumor (Fig. 16). Some cells were spindle-shaped, but others were irregular. The cytoplasm was distinctly outlined and deep pink, and the nuclei were irregular and extremely hyperchromatic. The cells were widely separated by edema fluid and contained scattered leukocytes. Surrounding the islands of residual tumor, there were many ghost cells and some hemorrhage. The large blood vessels were dilated, and their endothelium was edematous. A few small arterioles were thrombosed.

RESULTS

Complete and permanent relief of local pain was obtained in each case, whether the pain was produced by intra-oral ulceration, or by invasion of bone. The period of time between the first injection and the relief of pain was not related to the dose given, but was consistently less than 48 hours. A sense of well being was noted within two days and persisted until radiomimetic and parasympathicomimetic symptoms appeared.

All accessible treated tumors showed gross changes during treatment. The borders of ulcerated squamous cancers became soft and flattened, while their central portions liquefied. Discharge was copious and surrounding induration diminished. After two weeks of treatment, increased vascularity and a decrease in size were apparent. In three cases, epithelialization of the ulcer was almost complete.

The non-ulcerated treated squamous cancers responded more slowly but decreased in size and became softer. If subsequent ulceration occurred, initial discharge of liquefied material took place with a resultant immediate decrease in size.

Radiomimetic changes occurred in all except the brain cases, in which little surface area was included in the field of treatment. Skin erythema and local edema appeared within 14 days and were most marked in those cases in which larger individual doses were used. When oral mucous membrane was included in the field of therapy, whitish patches (similar to roentgen ray mucositis) appeared within ten days and persisted until after treatment was complete. When scalp or beard areas were included in the field of treatment, loss of hair

occurred within ten days. Eye lashes and eye brows were not affected. This loss of hair could be prevented by compressing the artery supplying an area of scalp, during each injection of the HN_2 (Fig. 17). Loss of hair was delayed in areas bordering either on the midline or adjacent non-treated areas. When a parotid gland was included in the field of treatment, marked edema developed within seven days and persisted throughout treatment. The intensity of these radiomimetic changes appeared to be directly proportional to total dosage and inversely proportional to the duration of treatment. Of cases receiving the same total dose, those treated over the longer period had less intense reactions. Of cases treated over the same period of time, those receiving the largest total dose had the most intense reactions.

Parasympathomimetic effects were present in each case in which there was, within the field of treatment, an end organ whose response to parasympathetic stimulation was measurable. Increased salivation always occurred when HN_2 was injected into the external carotid artery but was limited to the ipsolateral glands. In one case, in which a large total dose was given into the external carotid artery, a miosis developed which could not be completely counteracted by the usual mydriatics. Skin areas within the treated region became warm and dry during the period of treatment and for several days thereafter.

Certain neuromuscular disturbances were noted, but the mechanism concerned in their production was not clear. We have chosen to consider them under the general classification of parasympathicomimetic effects. Convulsions occurred in two cases, but were secondary to anoxia following pulmonary embolus in one. In the other case they occurred immediately after the injection into the internal carotid artery of HN_2 and of Thorotrast. The injection of HN_2 into the internal carotid artery did not produce convulsions in the other patient, who received even larger single doses. Five cases developed marked weakness during the second and third week of treatment. In three instances, this was followed by the appearance of asynchronous fibrillary muscle twitching in all extremities and by marked prostration. At the same time, the pulse was not rapid, the extremities were warm and dry, but the blood pressure was below normal. The patients were lethargic but could be aroused and were oriented. These symptoms persisted until death occurred, which was associated with bronchopneumonia in one case, with massive aspiration of vomitus in the second, but with no known cause in the third.

The blood studies have been summarized in Table III. A significant leukopenia developed in only four patients, reaching a maximum between the thirteenth and twentieth day of treatment. The eosinophils always disappeared from the peripheral blood within four days and reappeared ten days following completion of therapy. A lymphopenia always developed within four days and persisted until at least eight days following completion of therapy. The degree of lymphopenia appeared to be proportional to the amount of HN_2 which was estimated to have passed into the general circulation rather than to the

amount in each individual dose or to the total dose administered. Partial mechanical block to venous return from the primary treated area seemed to decrease the severity of the lymphopenia and leukopenia, whether by bilateral removal of the efferent veins or by application of a venous tourniquet proximal to the site of injection.

An initial polymorphonuclear leukocytosis always occurred and persisted up to nine days. Toxic granulations appeared in the neutrophiles and were present throughout therapy. Vacuolization of monocytes was striking during the recovery phase, and numerous unclassified plasma cells appeared.

Cellularity of bone marrow was estimated and recorded as one, two, three, or four plus (normal). A depression of bone marrow occurred in all cases which received more than a total of 20 mg. of HN_2. It reached a maximum of one to three plus in seven to 31 days. Multiple injections in small doses produced the least depression. At the time of maximum depression, the marrow showed a high percentage of adult polymorphonuclear neutrophiles.

The red blood cell count and hemoglobin were not affected by therapy even though there was considerable depression of normoblast in the bone marrow. These patients have not been followed long enough to detect a late anemia.

All patients showed some depression of platelets, but none developed petechiae or purpura. The course of the platelets was extremely erratic, and no general statements are warranted.

Histologic changes occurred in all treated tumors which could be examined. In the squamous cancers, the first changes were observed on the second day of treatment and consisted of extracellular and intracellular edema of all treated cells except those in the epidermis. Subsequent biopsies showed increasing degeneration of the cancer cells, loss of nuclear details, cytoplasmic vacuolization, and thickening of the cell membrane. Mitoses became reduced in number, and many were abnormal in appearance. Keratin and debris appeared in increasing amounts. Thromboses occurred in some arterioles, but the veins and large arteries showed only endothelial swelling. The stromal cells showed slight edema and minimal degeneration. The basal layers of the epidermis showed slight edema and normal mitoses throughout therapy.

Progressive degenerative changes could not be observed in the case of the fibrosarcoma, since serial biopsies could not be taken. Sections removed at autopsy 22 days after the first injection, however, showed marked destruction of the cells, leaving only scattered islands of recognizable sarcoma which was in the process of cytolysis.

DISCUSSION

The treatment of a malignant tumor by repeated injections of a chemotherapeutic agent into its nutrient artery is a method of cancer therapy not previously described. By this method, an increased amount of HN_2 has been delivered to certain malignant tumors, and measurable changes have been produced which have not been seen to follow the intravenous administration of

the same drug. Since we have undertaken these studies, we have learned of the work of Shimkin,[21] who has obtained similar results following the single intra-arterial injection of HN_2 in patients with skin manifestations of a malignant lymphoma.

The regions best adapted to this type of therapy will be determined by the anatomy of the arterial blood supply. A tumor, located in an area whose blood supply is derived mainly from one artery, would be most suitable. Therefore, tumors occurring on an extremity or in certain areas of brain, head, neck and pelvis could be treated. Those occurring in areas within the thorax, upper abdomen and either thoracic or abdominal wall would probably require quite complicated technics. However, a tumor within a specific organ such as liver, might be treated, but this would first require a study of the possible toxic effects of the drug on each organ in question.

Detailed knowledge of vascular anatomy is necessary, as the entire tumor area must be included. Failure to define accurately the treated areas would and has resulted in either rapid recurrence of the tumor in an under-treated border zone, or failure to obtain any regression of tumor located just beyond the region supplied by the artery through which the drug is injected. The sharpness of the boundaries of the treated region is illustrated in the case in which the area of epilation on the scalp was confined to that supplied by the occipital artery, other scalp arteries being compressed at the time of injection (Fig. 17).

The ideal agent for this type of therapy may not be HN_2, which was the only drug employed in these studies. The ideal drug would be extremely toxic to cancer cells, but quite innocuous to adjacent normal tissue cells. It would be either completely absorbed by the tissues adjacent to the first capillary bed, or completely inactivated by the time it reaches the venous circulation. Few drugs have been studied with a view to defining these properties.

Methods are available either to increase the intensity of the regional effect, or to decrease severity of systemic toxic effects. Application of a venous tourniquet proximal to or ligation of veins efferent from a treated area should increase both the circulation time through the first capillary bed, and the intracapillary pressure, and thus increase both the amount of the drug delivered to the tissues of the first capillary bed, and the time during which de-toxification could take place. These methods were used and it was our impression that they were effective. Intravenous injection of a non-toxic antagonist at the time of each intra-arterial injection of the chemotherapeutic agent should reduce the toxic systemic effects of the agent. Such use of sodium thiocyanate as an antagonist to HN_2 has been suggested[2] and has merit. The use of a heart-lung mechanical pump to maintain the circulation of an isolated tumor-bearing extremity during the period of therapy would prevent action of the drug on the remainder of the body.

All these methods should be evaluated. The presence of the tumor itself may have a protective effect. Adair and Bagg[1] treated a few malignant tumors

in human patients and animals by local application of mustard gas. They noted that the presence of a malignant tumor seemed to afford some degree of protection again large doses of mustard gas. It was also our impression that the patients whose treated regions contained the largest tumors had less systemic toxic effects from the HN_2. It is also important that this be determined accurately.

Neither the optimum total dosage nor rate of administration of HN_2 has been determined. Almost universally, total dosage only has been considered in studies of total body cancer chemotherapy. Considering the analogy that the effectiveness of radiation therapy has been increased by either repeated small doses (Coutard X-ray Therapy) or by continuous therapy at a lower intensity (interstitial radium therapy using low intensity needles), it would not be unreasonable to assume that a dosage schedule is of considerable importance in regional cancer chemotherapy. It has been our impression that regression was slower, but that toxic action on regional normal tissue was less, when the intervals between treatments were 12 to 24 hours, than when the intervals were eight hours. However, long intervals between injections increased the total time during which the arterial cannula had to remain patent, and thus increased the technical difficulties in delivering a maximum total dose of drug. It is important to determine the optimum intervals between injections and the advisability of using continuous slow, intra-arterial perfusion.

The possible advantages of this type of therapy are great. If complete chemical control of the local regional cancer were possible, some extensive operations could be avoided. If only partial control of the local cancer were possible by regional chemotherapy, supplementary roentgen ray therapy might be used to complete the treatment.

The synergistic action of HN_2 and roentgen rays has been demonstrated to apply to total body therapy; therefore, regional roentgen ray therapy as a supplement to regional chemotherapy should be equally effective. Serial biopsies of accessible treated cancers have demonstrated marked destruction of tumor cells and changes which are almost indistinguishable from those following treatment with cancercidal doses of roentgen or gamma rays.[11, 25] Observation of changes in the gross appearance of ulcerated cancers during treatment have yielded similar results, while skin changes in adjacent treatment areas have been minimal. Much can be learned by further studies of this "chemical radiation." There is a suggestion that malignant tumors which are insensitive to radiation may be sensitive to the effects of regional chemotherapy. This was demonstrated both in the case of the fibrosarcoma which had shown no apparent response to external irradiation, and in the case of the squamous cancer, recurrent after a full therapeutic course of local external irradiation. Both of these cases showed regression following regional HN_2 therapy.

Our initial results are encouraging. Local pain, due to tumor, was relieved at once and did not recur even in those patients who survived several months.

Complete autopsy studies are now available of the first two cases treated. In one case there was neither gross nor microscopic evidence of cancer within *the treated region*. There was untreated and metastatic cancer in other regions of the body.

Our experience has been limited and, until many of the problems mentioned have been solved, regional intra-arterial cancer chemotherapy must be considered as an experimental procedure. By injudicious use of this method, one could produce necrosis of all tissue within a treated region. No rules as to dosage or schedule of treatment can yet be formulated. Because of the encouraging initial clinical results, further studies should be undertaken in suitable institutions.

SUMMARY

1. A method of regional cancer chemotherapy is described.

2. The intra-arterial injection of HN_2 produces within the area supplied by the injected artery, a more intense tissue reaction than can be produced by the intravenous administration of lethal doses of the same drug.

3. HN_2 administered intra-arterially in repeated small amounts, has been shown to have a selective action on neoplastic tissue within the area supplied by the injected artery. Gross and microscopic evidence of regression has been demonstrated in clinical areas.

4. Animal and clinical studies are included in this preliminary report.

The authors wish to express their appreciation to Dr. Brian Blades, in whose laboratories most of this work was conducted; to Drs. Harold Stewart and Murray Shear and members of their departments for their suggestions and aid in preparing the manuscript; to Dr. Shields Warren for his encouragement and advice; and to Dr. John Hoyle for his editorial aid.

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CARCINOMA OF THE BREAST

FIFTY YEARS EXPERIENCE AT THE MASSACHUSETTS GENERAL HOSPITAL

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AT THE MEETING of the American Surgical Association held in Washington, D. C. on May 7, 1907, there was a symposium on the results of operations for carcinoma of the breast. Doctors Greenough, Simmons and Barney were invited to present the results of cases treated at the Massachusetts General Hospital between the years 1894–1904. This was the first—whereas the present communication is the ninth—of a series of reports of end results in cases of carcinoma of the breast at this Hospital. The total experience involves about 2500 primary cases, of which approximately 2000 were submitted to radical mastectomy. In the more recent series, through the co-operation of the surgical staff of the Hospital, all private as well as ward cases have been included.

In computing "cures," all cases submitted to operation are included, except those who died of intercurrent disease, without recurrence, in less than five years after operation; these are omitted as inconclusive. Untraced cases, and patients living with recurrent disease or who are known to have died with recurrent disease after five years are classed as failures. Thus "cured" cases are those known to be living and free from evident recurrent disease five or more years after operation, plus those dying without recurrence after five years. These definitions must be borne in mind in comparing results with those obtained in other clinics, in some of which the five-year survivors are reported, whether known to be involved with active recurrence or not. It is, of course, well recognized that the use of the term "cure" is not justifiable. Simmons followed a group of the cases for ten years, showing the incidence of late recurrences. However, a ten year follow-up observation is very difficult to secure in a hospital population; and the number of cases lost to view or dying of intercurrent disease may impair the value of a longer term study.

Figure I summarizes the results that have been observed in the successive series of cases.

The most significant fact brought out by the Figure is that each succeeding group fared better than the earlier groups. Numerous factors have contributed to the improvement.

Operability Rate. Throughout the half century, the radical operability has remained at about the same level, ranging from 72 per cent to 80 per cent of

* Read before the American Surgical Association, Colorado Springs, Colo., April 21, 1950.

all primary cases admitted to the hospital. A progressive sharpening of criteria of operability has tended to lower this percentage. The development of effective radiation therapy as a palliative procedure has justified omission of operation in the treatment of borderline and poor risk patients. The development of hormone therapy for this class may be expected to have a similar result. Offsetting these tendencies, improved methods of anesthesia, operative technic and preparation of patients for operation have permitted safer operations on more poor risk patients. However, the most significant fact making for higher operability is the increase in the number of favorable cases sent to the Hospital for operation. The disease is being discovered earlier, and the physicians of the community are referring cases more promptly for operation. Especially since the development of various institutions which are available for terminal care or palliative radiation, a progressively more favorable group is referred to our Hospital for operation. The ratio of cases without axillary lymph node metastases to the total group has definitely increased.

Criteria of Operability. The original report emphasized the unfavorable prognostic significance of a growth adherent to the skin or chest wall, ulceration and skin involvement, grossly enlarged axillary lymph nodes, palpable supraclavicular lymph nodes, bilateral involvement and the complication of pregnancy or lactation.

Further experience has borne out these findings. Indeterminate significance attached to the quadrant of location of the tumor in the breast itself. The poorer prognosis in younger age groups has been shown to be due to more rapid growth and generally higher grades of malignancy in youth. While the duration of the disease is of great prognostic significance in the individual case, this significance has been rarely demonstrable in analysis of groups of cases. The original study correlated the prognosis with the histologic type of growth, progressively improving from medullary carcinoma to scirrhus, to adenocarcinoma, to colloid. Lessened emphasis on these types has resulted since Greenough applied the principle of grading to breast carcinoma.

The use of preoperative roentgen ray examination to detect asymptomatic metastases, now employed almost routinely, has permitted more accurate definition of the group likely to benefit from operation.

The Operation. While the technic of radical mastectomy was well understood, and in large part followed, in the earlier series there were numerous exceptions and variations carried out. Sub-radical procedures, with preservation of part or all of the pectoral muscles, were often used. On the other hand, ultra-radical operations with removal of clavicle and supraclavicular contents were occasionally resorted to in attempts to control advanced disease. The futility of these procedures led to their gradual abandonment.

The first step toward standardization of the operation consisted in the assignment of the cases of breast carcinoma to individuals primarily interested in the problem. With the organization of a Tumor Clinic, the cases

were assigned to the personnel of the Clinic. More recently, the Clinic has had the responsibility of teaching the resident staff the principles and technic of radical mastectomy. The inclusion of the private ward cases in the recent reports has again introduced some variations in the details of operative technic, although the principles of the radical operation are well followed. The chief variation involved in inclusion of the private cases is the interpretation of operability. In recent series of cases, careful study of the descriptions of the cases has led to the conclusion that a certain number which were inoperable have been subjected to radical mastectomy. Thus in the present series, 12 such cases were operated upon in all of which the disease progressed to an early fatal termination.

Refinements in general surgical technic, preparation, anesthesia, and after care, have reduced the postoperative mortality from 3.6 per cent in the original series, to 0.65 per cent in the current series.

Better selection of cases and improved technic have improved the results in cases without axillary metastases as well as in cases with axillary metastases, as shown in Figure II.

Although very wide skin removal has not been carried out, and skin graft closure has not ordinarily been required, the incidence of recurrence in the operative field has decreased steadily, until in the present series it stands at 11 per cent. This incidence seems to be related to the grade of malignancy of the carcinoma rather than to the type of operation performed. Postoperative lymphedema of the arm has likewise diminished, and now occurs significantly in less than 10 per cent of cases. This improvement almost surely can be attributed to a more fastidious operative technic, control of wound infection, and the abstention from postoperative prophylactic roentgen ray therapy.

Extent of Disease. It is generally agreed that the presence of axillary metastases is a factor of utmost significance in prognosis. Figure III shows the percentage of survivors at six months intervals after operation in the present series.

It should be noted that the five-year survivors are greater in number than the five-year "cures," as defined above. The "cures" in the entire group are 51 per cent, including 77 per cent of cases without axillary node involvement and 33 per cent of cases with axillary metastases.

In recent years, greater thoroughness of search of the axilla by the pathologists has paradoxically resulted in improvement in surgical results. The more careful the search of the axilla, the more surely cases classed as free from axillary node disease represent a favorable group. At the same time, the transfer of a number of cases with minimal axillary metastasis to the group with axillary involvement will improve the results in the latter group. We have been able to verify again the observation that the degree and extent of axillary node metastasis is of great importance in prognosis. When there was specific notation of only one or two nodes involved in metastasis, "cures" resulted in 76 per cent of the cases.

Grade of Malignancy. Greenough defined criteria for grading the degree of maligancy of breast cancers, and demonstrated its significance in prognosis. Since the initial studies, the criteria for grading have shifted somewhat; resulting in fewer cases and an even more favorable prognosis in the Grade I cases. There has been correspondingly an increase in numbers and an improved prognosis in the cases of high grade malignancy, Grade III. Figure

FIG. 1

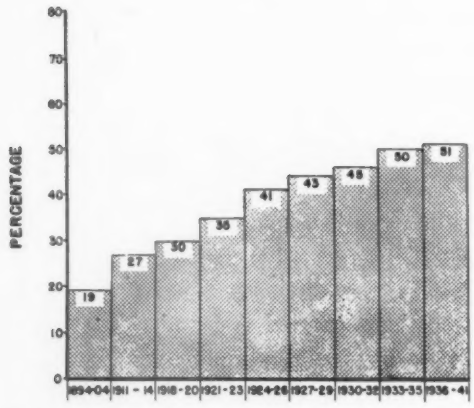
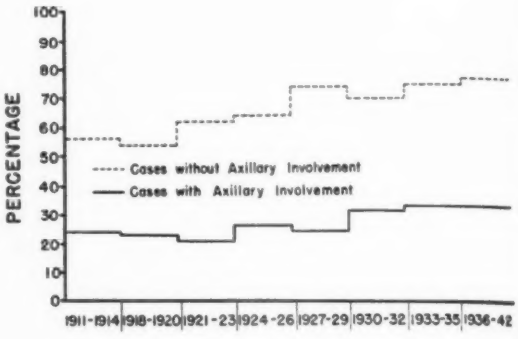


FIG. 2



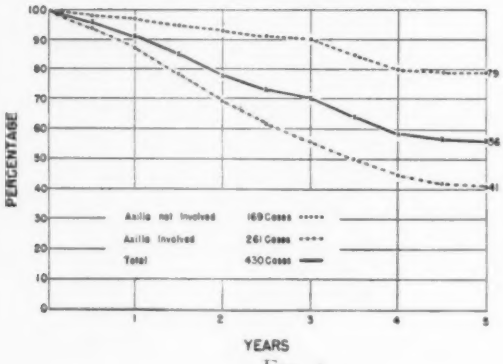


FIG. 3

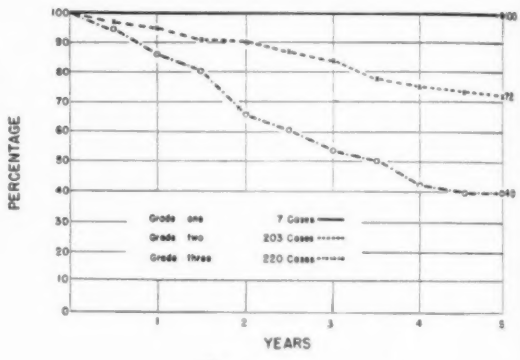


FIG. 4

FIG. 1.—Carcinoma of the breast; results of radical operation; percentage of five year "cures."

FIG. 2.—Carcinoma of the breast; percentage of five year "cures."

FIG. 3.—Carcinoma of the breast, 1936-1941.

FIG. 4.—Carcinoma of the breast, 1936-1941.

IV shows the percentage of survivors at six months intervals following operation in the various grades of malignancy. It was noted above that the proportion of higher grades in young women is greater than in older women. Axillary metastases take place earlier, and operative field recurrence is increased in the Grade III lesions.

Radiation Therapy. Occasional series of cases were submitted to preoperative or postoperative roentgen ray therapy during the period. None of this

therapy would be considered adequate according to present concepts. At no time was it apparent that the treatment as carried out was effective in increasing cures, or deferring or diminishing postoperative recurrences. Therefore, it has not been our custom to employ any radiation therapy, preoperatively or postoperatively as a prophylactic procedure. We do employ roentgen ray therapy in recurrent and inoperable cases, and in those instances when the surgeon is convinced that he has had to leave gross disease behind at the time of operation.

Hormones. The original report included a few cases of carcinoma in young women who were submitted to oophorectomy, without any demonstrable benefit. During the early 1930s a series of cases was subjected to prophylactic postoperative pelvic radiation to bring about an artificial menopause. These patients showed no significant improvement in the prognosis compared with a control series. Since that study, artificial menopause by surgery or radiation has been restricted to young women with recurrent or inoperable disease; and in many of these it has been of distinct although transitory benefit. In more recent years, the use of androgenic and estrogenic hormones has been added to the armamentarium in the treatment of recurrent and inoperable breast carcinoma. Here also, the effect in many cases is beneficial although transitory. It seems likely that survival time in recurrent cases will be prolonged by these measures.

SUMMARY

Definite improvement in the results of radical mastectomy at the Massachusetts General Hospital has taken place during the past 50 years. The improvement has been the result of better operative technic and more careful selection of cases. It is probable that a considerable part of the improvement has been the result of education of the public and the profession.

The presence and extent of axillary involvement, and the grade of malignancy seem to be the most important factors influencing the prognosis. At the present time radical mastectomy may be expected to result in a five-year "cure" in about half of the cases submitted to operation.

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DISCUSSION.—DR. GEORGE G. FINNEY: I have enjoyed very much Dr. Taylor's presentation, having been interested in this subject for some time. There are only two aspects upon which I would like to comment.

In the first place, in going over some cases recently, one case particularly came to my attention, which was operated on in 1922 with a radical mastectomy by Dr. J. M. T. Finney, Sr. By all pathologists it would be agreed it was a very malignant type of case. There were axillary metastases at the time of the operation. That patient is still perfectly well. That is an isolated case, but I would like to simply present that as one example where careful radical amputation was important in perhaps saving life, particularly in these days when there are reports of compromise in the type of treatment.

Recently, as you know, we had a report from Edinburgh, where simple mastectomy was advocated, with treatment of the axilla by radiation. Radiation and hormonal therapy certainly have a place, but in our present state of ignorance complete eradication—not only of the disease but the avenues over which it might spread—offers the best outlook at the present time.

Dr. Taylor spoke of five-year cures. I can't help but wonder if we might not be more accurate in following the terminology of our tuberculosis friends, and if we should not speak of arresting the disease for such-and-such a time. In going over series of cases, so often we will have cases which are free of disease as long as five, eight, ten and 15 years or more and then develop metastases.

In one case that I know of, there was a lesion of one breast which later developed what must have been a reactivation of the disease in the region of the scar, some 17 years after the original operation.

DR. ARTHUR B. MCGRAW: I wish to add a few words in support of one of Dr. Taylor's last remarks in this very interesting paper, namely, that with regard to the necessity for further efforts at education.

With the amount of propaganda in regard to cancer and cancer detection that is being spread before the public nowadays, it seems to me there can be but very few

intelligent women who are not acutely aware of the possibility of cancer occurring in their breasts.

I do not think that teaching them to be prompt in consulting a surgeon when they detect a breast lump is nearly enough. Women should be told to examine their breasts at those intervals.

If they examine their breasts once a month, gently and thoroughly, I think they will have at least some chance of picking up a really early growth. If they are only alert to consult a doctor when they happen to discover a growth the duration of that growth is uncertain and metastasis may well already have occurred.

DR. WILLIAM CRAWFORD WHITE: I enjoyed Grantley Taylor's paper very much. It has been a wonderful privilege to have followed their work for so many years.

I, too, have been interested in following groups of cases, and have been rather puzzled by the difference in the reports from various clinics. I am sure that all of you have had a similar experience.

One man I know reported, in England, that he had 84 per cent 5-year survival in localized cancer. He used the word "survival." How does he do it? I think that rather than make any carping criticism, I would make a strong plea that some organization such as this or the American College of Surgeons—of which Dr. Taylor is Chairman of the Cancer Committee—set up standards so that we could have more or less uniform reports. That is certainly not true at the present time.

I think that in some respects Dr. Taylor is a little harsh on himself. But perhaps he hasn't been so harsh, in that maybe he has chosen not to operate on some cases that other clinics would have chosen.

I think Stout's and Haagensen's criteria are very fine in many ways. All of us are familiar with their paper, but I think that if we follow their standards too rigidly, we will lose some cases, that, given a chance, would survive.

For example, this is particularly true of their attitude toward pregnancy. We have had a case of cancer of the breast, discovered at six months. The patient was subjected to radical mastectomy, and allowed to go to term. This patient is in good health eight years later.

My chief purpose in discussing this paper is to urge Dr. Taylor and his committee to do something about our standards and methods of reporting.

DR. OWEN H. WANGENSTEEN: At last year's meeting of the Association (Tr. Am. S. A., **67**: *27*, 1949), I reported briefly upon extension of the Halsted operation for patients having cancer of the breast with axillary metastases. Since then, sufficient experience has been acquired with the procedure to warrant a further statement. The modern operation for cancer of the breast was standardized by Halsted more than 50 years ago, the procedure as he described it representing essentially the composite ideas of many men. Today, it should be said, I believe, the Halsted operation for cancer of the breast is outmoded: it is not radical enough; it is an incomplete operation for cancer of the breast in patients exhibiting axillary metastases.

The extension of the conventional Halsted operation as I have been doing it consists of the following additional items done simultaneously: (1) a supraclavicular dissection, performed with the clavicle retracted laterally; (2) excision of the internal mammary chain of vessels and the intercostal lymph nodes lying in juxtaposition to the vessels; it has been feasible to remove simultaneously, too, the contralateral chain of internal mammary vessels; and (3) a mediastinal dissection.

In the first two patients operated upon, the inner one-third of the clavicle was removed. Neither the patients nor I liked the deformity. Subsequently an intramedullary inlying Kirschner wire was employed; non-union resulted not infrequently. Later, the clavicle was rewired and the patient wore a clavicular cross during the early weeks after operation. Non-union was still observed. Now, for several months, I have been

doing a median sternotomy, removing the first rib, and utilizing the opportunity to make the best possible axillary, supraclavicular and mediastinal dissection. An extrapleural cut is made into the first interspace to facilitate removal of the first rib. The median sternotomy is then continued into the fourth interspace. On completion of the dissection, the sternum is rewired. This mode of gaining access to the mediastinum has proved eminently practical. Moreover, the wound heals kindly and with none of the difficulties encountered in dealing with the problem of osseous union following division of the clavicle.

Any number of a variety of skin incisions may be employed: the one I prefer is a low oblique cervical incision, starting not too far laterally, which reaches the midline just over the manubrium sterni, and continues down in the same direction almost to the xiphoid process. The breast is removed through an oblique to elliptical skin incision, the outer end of which courses upward toward the axilla. Ordinarily, the median sternal skin incision and the lateral component through which the breast is excised do not quite meet; a short bridge of skin separates the two incisions and not infrequently, the contralateral breast has been simultaneously removed through a similar transverse incision on the opposite side. My colleague, Dr. T. Brannon Hubbard, has been subjecting the contralateral breast, sacrificed in this manner, to careful scrutiny. During the brief time that this study has been under way, three unsuspected microscopic cancers have been found in the contralateral breast. A palpable lump, even in 1950, is the earliest sign of a cancer of the breast! Whereas I deplore that circumstance, I know of no better way to recognize breast cancer. We are beginning to appreciate that cancers which cause symptoms in the alimentary tract have probably been present approximately two years. May not a palpable breast cancer, too, have been present for just as long? As far as we know there are no local precursors of breast cancer. Certainly then, more often than is our custom, the contralateral breast should be removed, when operating for cancer of the breast, for in all likelihood, the systemic cause which provoked the first breast cancer continues to operate.

As the accompanying slide indicates in the mediastinal dissection, the homo- and contralateral innominate veins can be cleared of lymphatic bearing tissue; on the left side, the thoracic duct is identified, divided, and ligated. The superior vena cava is stripped of lymphatic tissue. The thymus is removed, and any lymph nodes identified in the anterior mediastinum are excised. Laterally, the fatty tissue over the medial aspect of the pleural sac of the homolateral lung is removed, and the dissection is continued down to the superior border of the pulmonary artery. Care is observed to avoid injury to the vagus and the phrenic nerves. The arch of the aorta and the vessels emerging from it are bared in the dissection.

This operation can be done without opening either pleural sac. I have the impression, however, that air may be sucked through the thin diaphanous mediastinal pleura without a visible opening having been made in the pleura. Because of this, and because of my anxiety to remove any fat lying along the internal mammary vessels upon the pleura, I have come to prefer to insert a temporary drainage tube, attached to suction into each pleural cavity. Moreover, a similar catheter placed in the mediastinum and brought out through the supraclavicular area on the contralateral side insures a dry mediastinum and eliminates any suggestion of widening of the mediastinal shadow, as observed on x-ray films during convalescence. Furthermore, these adjunct measures simplify postoperative care with reference to need for postoperative aspiration of fluid.

A wide removal of lymph nodes and lymphatic bearing tissue from axilla, neck, and mediastinum, including the internal mammary chain of vessels bilaterally, is permitted in this dissection. Obviously, it is a more complete operation for breast cancer than the Halsted operation for breast cancer; only time will tell. Approximately 60 per cent of patients with breast cancer, having axillary metastases, submitted to the type of operation depicted in the slides shown, exhibit evidence of cancer beyond the reach of the conventional radical operation. Such metastases have been observed in

the internal mammary chain of lymph nodes, in the mediastinal lymph nodes and in the supraclavicular area.

In the light of Saphir's studies (Cancer, **1**: 288, 1948), in which microscopic study by the serial section method of the axillary lymph nodes demonstrated that 30 per cent of patients undergoing axillary dissection for breast cancer actually had cancer in the axillary lymph nodes, when by routine hospital laboratory examination they were negative—in the light of this circumstance, certainly no contraction of the operation for breast cancer is in order, as is being currently urged again. Moreover, Andreassen and Dahl-Iverson (Journal Internationale de Chir., **9**: 27, 1949) in doing routine complemental supraclavicular dissections together with the axillary dissection have observed the frequent presence of microscopic cancer in the supraclavicular lymph nodes. They, too, employed the serial section method and found cancer to be present in 34 per cent of patients in supraclavicular lymph nodes when demonstrable axillary metastases were present. Will the time come when it will be considered justifiable to perform the type of operation illustrated in the colored slides which I have just shown you for all breast cancers? I am not prepared to answer in the affirmative today, save for those in whom axillary metastases are found at operation. For all cancers located in the median half of the breast it might be well to contemplate its performance. Actually, the Halsted operation is an incomplete operation for breast cancer.

Dr. Cranston W. Holman: Dr. Taylor, our results have not been influenced by the use of x-ray therapy. As a matter of fact, we have had several very unpleasant and distressing complications following its use. I refer particularly to the postoperative swelling of the arm that occasionally occurs.

Drs. McSwain and Beal made a report some time ago on the percentage of cases of postoperative swelling of the arm, and they found that approximately eight per cent had swelling that was somewhat distressing. In all of these patients, x-ray therapy was given, and the patient also had a minor infection of the wound.

In following our patients, we found that there were several rather interesting cases who developed swelling of the arm quite late after the mastectomy, and this swelling developed coincident with a minor infection of the hand, or the fingers. As a result of that experience, we now advise patients about the care of their hands, just as we do the diabetic about the care of his lower extremities.

Dr. Taylor should be congratulated on this remarkable follow-up.

Dr. Joe V. Meigs: We have been impressed by the work that you have done, Dr. Taylor. You have produced through all these years a series of cases that is of the most inestimable value to all of us.

After hearing Dr. Lahey's and Dr. Marshall's paper yesterday, and now Dr. Wangensteen today, I am prompted to say that we may be carrying surgery too far. It seems to me that before we advise such surgery we should call for help from the pathologists.

It is obvious that there are extending and invading cancers and that there are metastasizing cancers. I can't help but believe that some of the patients operated upon by very extensive procedures and given some palliation, who have had widespread growth of their disease, have tumors which—although they look microscopically or histologically like another cancer—may be quite different. Perhaps by histochemical means, perhaps by utilizing the work of Harry Green of Yale in attempting to grow, by transplanting them, tumors in the eyes of animals we may be able to differentiate between those patients who should have extremely radical surgery and those patients who should not be operated upon at all. Certain patients probably need only to have their tumors and nearby lymph areas removed.

I am sure in my own mind, having operated upon a number of patients by very radical pelvic surgery—taking out bladders, rectums, and all pelvic organs—that some

of those tumors are local and not metastasizing. They might have been radiation-resistant and if we had operated on them and had not trusted to radiation we might have cured them, without having to remove all of the pelvic organs. In 40 per cent of these advanced cases no positive nodes are found.

The pathologist is going to give us the most help in the future. It is necessary to be radical but I feel sure that living pathology is essential. Why do certain patients with the same type of tumor or disease die and certain ones live? Why do certain patients have nephritis, for example, and others not?

The question of early diagnosis is extremely important. Fortunately, in the field of gynecologic surgery—due to the fact that the cervix can be seen and felt, can be biopsied, and smears can be easily obtained—we have improved the chances of finding early cervical cancer.

This year Nelson's Surgical Monographs will contain five papers on carcinoma in situ. In those five papers alone 645 carcinomas in situ will be reported. In about one-half of these cases the vaginal smear has played an important role. This is extraordinary but can be done. All these patients who have had adequate surgery are living.

Dr. Edward D. Churchill: I agree with Dr. Wangensteen to the extent that if anyone wishes to extend the Halsted operation to the supraclavicular area, the midline sternotomy incision is an excellent approach.

Having studied the topographic anatomy of this area, I recognize what may be called certicothoracic surgery—an entity just as important as abdominothoracic or thoracico-abdominal surgery. The midline sternotomy with lateral extension above as a collar incision in the neck, and lateral extension below in a selected intercostal space, affords excellent exposure. It is not necessary to divide the clavicle. I have found it very helpful for tumors of various types that occur in this region.

I have employed this approach recently on a patient with a single palpable lymph node found above the clavicle two years after a radical mastectomy. Free access is afforded from the inner margin of the first rib to the hilum of the lung. In this case many involved lymph nodes were displayed—too many to afford any hope of arresting the disease.

In other instances the great venous trunks have been removed, taking the subclavian as it crosses the first rib, the internal jugular as high as desired and the innominate down to its juncture to form the superior vena cava.

But we should remember that the basic principle of the Halsted operation is to remove *en bloc* the lymphatic pathways that lead to the nodes, and not rely solely on the ablation of embolic foci that have been established in nodes. In the patient referred to above, there was extension via the internal mammary route. It was easy to strip off the internal mammary vessels and remove them at the subclavians, but in the third and fourth intercostal spaces near the border of the sternum, there were small plaques of infiltrating cancer—not nodes.

A block resection that includes the inner ends of the costal cartilages, the perforating lymphatics that surround the branches of the internal mammary vessels, and the outer margin of the sternum will be required.

Adequate cancer surgery is not based on picking out lymph nodes. As Mr. Allison pointed out yesterday, the areas of fascial plane permeation in lymphatics comprise a basic consideration.

Dr. Grantley W. Taylor (closing): At the risk of prolonging this too long, it seems to me I must comment on some of the remarks made by the discussers, for which I am grateful, and to whom I am grateful.

Dr. Wangensteen offered us some challenging remarks, as he always does, saying that the Halsted operation is outmoded. What I think we hope to accomplish is to popularize the Halsted operation. We are still having patients sent in to the Massachusetts General Hospital—in all too numerous groups—who have had the removal

of a lump, or who have had a simple mastectomy three weeks before, and we are asked to "please treat with x-ray."

Now, by expanding the limits of surgery, we may effect the salvage of some of those cases, which, in my opinion, have primarily gone beyond salvage, but we are not going to do much more. We're going to accomplish much more by popularizing the Halsted operation, and insisting that it be done in every case.

Dr. Finney touched upon the recent apostasy of McWhirter of Edinburgh. I think it is terribly deplorable to have anybody like that coming along and offering, in my opinion, a retrogressive heresy of that kind. I am afraid that Dr. Wangensteen's remark that Halsted is oumoded will be seized upon by incompetent or narrow-minded or close-minded individuals, further to undermine the possible benefits which may derive from a widespread popularization of the proper operation at the present time.

I don't decry Dr. Wangensteen's experiments. I think that the attempts to push forward the frontiers of surgery in all directions is an extremely wholesome thing. We will follow his work with a great deal of interest, and when he reports his five-year results on this particular group, it will be very impressive to see what he has actually accomplished beyond the proof that such surgery can be done with survival and without seriously handicapping the individual.

Dr. White brought up a question which I think I might have covered more, at length, concerning the standardization of methods of reporting end results.

The American College of Surgeons has a subcommittee concerned with making recommendations in this very field. They are attempting to bring about a unison of opinion with the American Cancer Society, with the League of Nations, and with the United States Public Health Service—in fact, with all people who are concerned with preparing cancer statistics.

Dr. Ernest Daland of Boston is chairman of that subcommittee of the College of Surgeons. He has had numerous meetings with other members of the group and with the other groups, and I am extremely hopeful that he will bring in a recommendation at the next Clinical Congress in Boston which will have the sanction and approval of the various boards concerned with statistical reporting, so that it can be promulgated. The present system, as Dr. White says, is rather chaotic, and frequently misleading, and if we can get a concerted opinion, even if it may not be the ideal system, at least it will permit comparisons to be made.

Dr. Holman touched on one point about late hand infections, as giving rise to lymphedema. I have only one minor comment to bring in there, and that is that I have seen the same sudden onset of rather marked lymphedema after a long period without any lymphedema by undue exposure to sunshine. Women go out on the beach two years or three years after a radical mastectomy, and get a severe burn. It causes a tremendous outpouring of lymph with lymphedema of the arm; the return circulation of lymph is inadequate, and from then on those people are saddled with a lymphedema. I think it is worth while to caution them not only to take care of their hands but also to keep out of the sun.

Editorial . . .

Guild Medicine

Medical men do not like to be considered tradesmen, nor to have their profession reduced, even in discussion, to a simple craft. Yet the medical profession, of this country at least, is not dissimilar in organization to the medieval crafts. The old merchant guilds were broad over-all organizations of men who were not strict specialists, and this may be said to correspond to our county medical societies. They sought to be all inclusive, and to control practices by moral authority when they lacked the backing of civil law. They made it difficult or impossible for non-members to survive economically, by controlling the means of livelihood. As specialization grew with expanding technical advances, craft guilds of specialists arose. At first these functioned beside the older guilds as out-growths of them, and many men belonged to both. Eventually the merchant guild was superseded. Is this a comparable development to our specialty boards?

The purposes of the craft guilds were threefold: first, to protect the public, ensuring the quality of their product; second, to standardize and improve the training of apprentices and to confer the master's title upon those who completed the required training and were able to demonstrate adequate competence; and third, to protect themselves from the competition of men not so qualified, by denying to them, or strictly limiting, the opportunity to compete. The first two of these purposes are explicit in our boards. The third is explicitly denied, but is implied in many statements describing the value of the certificate, and in practice has already, in many instances, become a reality.

How, then, did these high purposes work out in the case of the guilds? There is little question that standards were elevated thereby for a long period. The rigid inspection of the products sold not only protected the customer against fraud, but also price control protected him against overcharging—a function our boards have not yet assumed. The apprentice and journeyman was protected against exploitation to a degree that might be envied by our residents, for in most cases an apprentice could appeal to the guild for a change of masters if he felt himself ill-used, and the guild undertook to find him another.

The guilds were frankly and openly monopolistic. They set rigid walls about each specialty, and divided and subdivided themselves to enormous complexity. The resulting restriction of individual initiative was stultifying, and led to an inelasticity which was a major factor in their downfall. For when a man can do only one thing, he must defend that activity at all cost. The same tendency is already visible in the boards.

Ostensibly the boards avoid monopoly. The number and subdivisions of

the Boards increase year by year. The fourth edition of the Directory, published in 1949, lists 16 boards. Eight of the 16 insist on strict limitation of work to the specialty, but only two attempt to define the limits of that specialty, and these bring out curious discrepancies. Thus a gynecologist may perform any abdominal operation on a woman, but may not touch a man, nor may he be trained by a surgeon. An otolaryngologist may practice ophthalmology, and must demonstrate skill in facio-maxillary (*i.e.*, plastic) surgery, and in any operation on the neck—but must not touch the thyroid gland. On the other hand, training to meet board requiremens in plastic surgery is so restricted that few otolaryngologists can obtain it. Ophthalmologists, however, have no restrictions. We are still in a formative period: will the lines be drawn sharply?

The tendency to prolonged and increasingly rigid training periods and requirements, so characteristic of the guilds, has already appeared as a result of well-intentioned effort to improve standards of teaching. Happily, it is a well-recognized danger to Board members, but its unfortunate effects are none-the-less apparent. In many specialties men accept prolonged "apprenticeships," not so much in order to learn more, as to meet specified requirements. Hospitals, too, are driven to inflate their programs in order to qualify in the competition for the trainees they need, but the "apprentice" in this case has no direct redress. This tendency is inevitable as long as the number of good training centers is inadequate to answer the demand for training. The other answer, in the form of "postgraduate courses," often tinged with commercial motivation, is not an altogether happy one. Will we, then, fall into the error of the guilds and so restrict the numbers who can attain to mastery that within our own ranks we promote dissension? Is the as yet unofficial Board of General Practice the first step towards a journeyman's guild?

It took about five centuries for the guilds to break down, but for the last two of these, their deterioration was apparent. In this slow-motion decay we can examine at leisure the factors which brought it about and so detect, perhaps, similar factors which may already be at work in our faster-moving times. The first was the change from the technical master to the capitalist. Enterprising masters began to find it easier to increase their production, and their income, by employing others, not merely as apprentices or assistants, but in groups of inter-related specialists who could act as a unit in turning out a product no one could alone produce. The resultant economy of operation concentrated the profits at the top. So companies were formed of diverse guildsmen, who looked to the company rather than the guild for their security. So industrialization and capitalism were born. This development was enormously enhanced as the means of production became too complicated and expensive for the individual master to own. Could we find in the modern "clinic" the counterpart of the happy company of fifteenth-century Jack of Newbury, of whom the ballad says:

"Within one room being large and long
There stood two hundred looms full strong
Two hundred men, the truth is so
Wrought at these looms all in a row
By everyone a pretty boy
Sate making quills with mickle joy."

The guild's reaction was in the direction of further monopoly. For this end they proceeded (a) to limit the number of apprentices, (b) to raise the fees for membership, (c) to add to the expenses of membership—especially the costs of feasts and production of mystery plays—their form of public relations expenditure, foreshadowing our radio and television broadcasts. Ruin came as the mass of craftsmen were prevented from starting for themselves, remaining as journeymen outside the guild or as powerless members within it, shirking office and even attendance at meetings, leaving to an increasingly small group the burden of office, and the power to dictate wages and conditions of work. The journeymen then formed their own guilds, since few could hope to attain mastery, seeking to defend themselves against exploitation, for they now, as employees, were deprived of independent decision. The small oligarchy of masters no longer supported and defended the journeymen but instead abused their power to amass wealth at the expense of both the journeyman and the consumer, and so lost public sympathy. Finally, the power to regulate became confused with government, as the guild oligarchy took over civil control. This ultimately destroyed the guild, for government now took over its function, its revenues, and deprived it of all control of the quality of production, of prices, and even of apprentice training.

Thus the beneficent craft guild was destroyed, first by the impact from without of industrialization which the guild answered by tightening its monopoly at the expense of its own source of strength—its trainees—to a point where public sympathy was lost and government was constrained to take over control. Is there a comparable development possible in our organization?

As long as the doctor depended on his senses and the few tools he could carry in his little bag, he was an independent practitioner who could not be industrialized. Great masters were developed, who attracted and trained many disciples, all of whom could hope to attain like mastery, but in order to do so the master could not lose touch with the stethoscope or the scalpel. He had to remain a master practitioner. With the development of more scientific medicine, there came more complicated tools. A practitioner now may own his electrocardiograph, his cystoscope, or even his X-ray apparatus, but who can be equally proficient in the use of all of them, and who can buy a betatron? Even an adequate battery of surgical implements is no longer economically practicable. Inevitably the more complicated and expensive tools of scientific medicine must be pooled for joint use, as well as the

increasingly complex array of technicians to run them. Thus the basis of industrialization already exists.

At the same time the interdependence of specialists forces cooperative effort and paves the way for replacement of the self-sufficient master by the modern equivalent of Jack of Newbury with his 200 happy weavers, their boys and their hand-maidens. How long will they remain happy? Jack makes a pretty penny, but he relies, in his primitive factory, on the skill of weavers trained by masters of the old regime. As soon as these become employees at varying technical levels, instead of masters in their own right with journeymen and apprentices under them who can in turn look forward to mastery, the happiness fades and fatal dissension enters. Nor is this tendency confined to the overtly commercial clinics. Even in teaching centers the same forces are at work. The modern University Hospital teaching center is even more complex, more interdependent and more expensive than the commercial clinic, for it must develop and try out the tools of the future, as well as carry the training of future masters to completion. As the economic pressure tightens, the economics of industry are called more and more into play, and with the economics, also its methods. The generous public no longer supports the generous University which in turn returns to the community the generosity of its academic wisdom. Instead the public is expected to pay its way, and efficient administrators, remote from the patient, determine alike his treatment and the destiny of those who treat him. Even the ethics of the individual become corrupted by the ethics of the institution, which does not hesitate to "sell" the public on the dangers of this or that disease, employing the most skillful professional money-raisers, that they may hire the most skillful medical talent.

Against this tide the guild-like boards are struggling, fighting to maintain standards of skill judged by performance rather than by publicity, and fighting to maintain standards of training which will perpetuate that skill. It is possible that they may succeed, but they will not do so if they fall into the same errors which destroyed the guilds. With the best intentions they have set up an oligarchy and are beginning to set up compartments of vested interest. Already they have tilted with Jack of Newbury, and have won. But the cry of monopoly and restriction of opportunity is already in the air. If they are to succeed in their high purpose, they must counter this cry. They must honor ability and skill, however acquired, and must not so codify and restrict specialization that the vigorous hybrid will be excluded while the inbred products of a dying specialty are maintained. They must judge training by the skill it produces, and not skill by adherence to a formula of training. Above all they must avoid the implication that as they sit in judgment, they also sit in control.

And in the meanwhile, what of the public? The prestige of medicine is high, but in his loss of self-sufficiency, the individual practitioner seems increasingly ineffectual. The medical house seems to be in disorder, and the patient feels somehow cheated and exploited by forces he cannot understand.

Somehow the fruits of the discoveries about which he reads so avidly and inaccurately are being denied to him. They must be made available, he feels, by the government if necessary. For if control is to slip from the patient's hand in his personal privilege of selection of a doctor, and his personal ability to pay, then he would rather see it fall to an agency over which he has at least the illusion of control, than to either an irresponsible industrialist, no matter how loud he shouts, or to a guild-like oligarchy whose standards he cannot understand.

GEORGE H. HUMPHREYS, II

ANNOUNCEMENT

A Symposium on Burns will be held in National Academy of Sciences Building, Washington, D. C., November 2, 3 and 4, 1950. The symposium was arranged by the Division of Medical Sciences of the National Research Council at the request of the Research and Development Board, Department of Defense. Five morning and afternoon sessions will be held, the program terminating at noon November 4. At these sessions 20-minute talks on all aspects of burns and burn therapy will be presented by outstanding authorities in the field. While advance registration is not required those planning to attend are urged to notify The Secretary, Division of Medical Sciences, of their intentions.

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY.

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Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY

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